PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/415, 9/70, 9/127

A1

(11) International Publication Number: **WO 99/63997**

(43) International Publication Date: 16 December 1999 (16.12.99)

(21) International Application Number: PCT/EP98/06656

(22) International Filing Date: 5 October 1998 (05.10.98)

(30) Priority Data:
09/096,294 11 June 1998 (11.06.98) US

(71)(72) Applicant and Inventor: JANOV, Arthur [US/FR]; Latitude 43, F-83900 Saint Tropez (FR).

(74) Agent: BREESE-MAJEROWICZ; 3, avenue de l'Opéra, F-75001 Paris (FR).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: USE OF CLONIDINE FOR TREATMENT OF ADDICTIONS, EPILEPSY, SLEEP DISORDERS, EATING DISORDERS AND MIGRAINES

(57) Abstract

Clonidine (or derivatives or compounds thereof) is used pursuant to this invention for treating epileptic attacks (frequency and strength), obsessive compulsive disorders, addictions (such as smoking, drinking alcohol and taking pain killing drugs both legal and illegal), migraines post traumatic stress syndrome, waking up many times during the night with nightmares and bad dreams, racing mind, hyperactivity, short attention span and inability to focus and concentrate, impulse neuroses such as chronic masturbation, voyeurism, exhibitionism, and rape, violence, temper tantrums and uncontrollable aggression, phobias, sexual problems such as frigidity and premature ejaculation, psychosis and severe emotional disturbance, borderline neuroses, physical affliction such as angina, palpitations and irregular heart beat, colitis and ulcers, and as an aid to psychotherapy. The clonidine can be administered transdermally (via a patch), orally (via a pill), parenterally (via a hypodermic injection), or rectally, or a combination thereof. It can be administered together with other drugs, such as ritalin or low doses of Prozac, and with other treatments, such as psychotherapy including Primal Therapy. The clonidine can also be administered by liposomal delivery systems, either nasal spray or salve. This has a more immediate effect and would be the mode of choice for those who sense a migraine coming on or a seizure approaching.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

USE OF CLONIDINE FOR TREATMENT OF ADDICTIONS, EPILEPSY, SLEEP DISORDERS, EATING DISORDERS AND MIGRAINES

Cross-Reference to Related Applications

This is a continuation-in-part of copending application, Serial No. 08/864,706, filed May 28, 1997, which is a continuation-in-part of copending application, Serial No. 08/812,007, filed March 5, 1997. The entire contents of both of these applications are hereby incorporated by reference.

Background of the Invention

There are many ailments and afflictions today that involve pain, both emotional and physical. The proliferation of pain medications, over the counter, such as Advil, Motril, and aspirin, and prescription drugs, such as Valium, Haldol, Prozac, Paxil and Zoloft, are ultimately designed to handle pain and suffering. Many new drugs, particularly the last three mentioned, are aimed at increasing the amount of circulating serotonin in the brain system. This accomplishes enhanced neuroinhibition and thus, better repression of pain and suffering. The tranquilizing drugs, the serotonin enhancers, for example, are used for a wide variety of ailments, both psychological and physical, as a tacit acknowledgment that pain is at the base of them -- from obsessive compulsive disorders to anxiety and depression, not excluding phobias and panic disorders. They may be used, as well, for migraines and high blood pressure.

Many of the prior art drugs decrease the transmission of the pain message across the synapse in a variety of neurochemical processes. The result is that the pain does

not get through to conscious awareness. It is not that the pain is eliminated; it is still reverberating on lower brain levels. Only the consciousness of it is diminished; that is, there is less cerebral "appreciation" of it.

Another more efficient way to handle these afflictions is to suppress the pain energy at its source, that is, to cap the traumatic imprint that causes the pain so that it cannot spread out in broad fashion throughout the brain. The release of the memory/imprint during sleep, for example, can result in recurrent nightmares or bad dreams; the identical content over months and years indicates that the same memory is there exerting a force toward the neocortex and limbic structures.

Summary of the Invention

There are basically two ways to deal with the symptoms discussed later. One is Primal Therapy, which is the systematic reliving of traumatic memories-imprints (from childhood) allowing them into conscious awareness in titrated doses which can be integrated in the neuro-biologic system. The other is through the introduction of an effective neuroblocker such as clonidine that keeps the memory imprint in its "box," so to speak. For those who do not enter Primal Therapy, clonidine is an effective suppressor of those elements which lie at the base of it all -- the brainstem structures of the reticular activating system, pons, medulla and locus ceruleus; structures which mediate traumas while the fetus is in utero. This will also include parts of the limbic system including the amygdala, hippocampus, hypothalamus and thalamus. It is these structures which are well formed before birth and which can, together with brainstem structures, process pains beginning in the first months of fetal life. (See "Imprints", by Dr. Arthur Janov;

published by Coward McCann in 1983, for the appropriate research.)

A. Composition Of The Medication

Clonidine has been used for approximately thirty years to lower blood pressure. There are other important uses for this medication, which are listed below. But first, one must understand how and why it works on the afflictions discussed below. Clonidine is an alpha 2 noradrenergic agonist. (See U.S. Patent No. 3,454,701 (Zeile et al.)) (This patent and all other patents and other publications mentioned anywhere in this disclosure are hereby incorporated by reference in their entireties.) It can be administered, for example, by a pill or a patch.

The patch is known as Catapres-TTS, a transdermal system distributed by Boehringer Ingelheim Company of Ridgefield, Connecticut, and manufactured by Alza Corporation of Palo Alto, California and licensed from Boehringer Ingelheim. See U.S. Patent No. 4,201,211 (Chandrasekaran et al.) The patch delivers clonidine at a constant rate for approximately seven days. It is placed on a relatively hairless section on the skin. There is a concentration gradient existing between a saturated solution of the drug in the system and the lower concentration prevailing on the skin. It flows in the direction of the lower concentration. Patches can deliver .1, .2 or .3 mg of clonidine. It is advisable to put a new patch on during the 24 hours prior to the final day of effectiveness of the preceding patch, in order to maintain continuity of dose. The stimulation of alpha 2 receptors in the brainstem results in reduced sympathetic outflow from the central nervous system.

Clonidine is a centrally acting antihypertensive agent. The 0.1 mg tablet is equivalent to .087 mg of the

free base. Clonidine hypdrochloride is an imidazoline derivative and exists as a mesomeric compound, the chemical name of which is 2-(2,6-dichlorophenylamino)-2 imidazoline hydrochloride. It is colorless, odorless soluble in water and alcohol. It acts rapidly reducing blood pressure after one to two hours of administration of an oral dose. The plasma level peaks in 3-5 hours with a half-life of 12-16 hours. Clonidine stimulates alpha adrenoreceptors in the brainstem reducing sympathetic outflow, decreasing peripheral resistance, renal vascular resistance, heart rate and blood pressure. During long term therapy cardiac output returns to predrug levels. About 50% of the absorbed dose of clonidine is metabolized in the liver.

It also stimulates growth hormone release in both children and adults but does not produce a chronic elevation of growth hormone with long-term use. It should not be withdrawn suddenly. Such cases may involve rapid rise in blood pressure and heart rate, plus elevated catecholamine levels in the plasma associated with irritability, headache and nervousness. Clonidine has been used in treatment of cases of children with short stature. (Pintor, C, Cella S, G. Loche, S. Lancet, May 30, 1987 1:1226-1230; see also compendium of International Symposium on Catecholamines and Stress, 1976, Edited by Usdin, E., Kvetnansky, R, Kopin, I., Pergamon Press, N.Y.; article by Jacob Korf, page 105, "Locus Ceruleus, Noradrenadline and Stress." (For Library use only); L.A.L. Fielding, "Progress in Clinical Research", pages 10-33 and 100, 130-166; K. Hayduck, "Symposium on Clonidine", Dec. 3/82 pages 49-53; M.A. Weber, Low Dose Oral and Transdermal Therapy of Hypertension, Steinkopff Verlag, chapter "Transdermal Clonidine in Essential Hypertension", by Groth H, Vetter H, Knesel J, and Baumgart P., page 60.

B. Additional Known Medical Uses Of Clonidine

Clonidine is useful for vasoconstrictor therapy as disclosed in U.S. Patent No. 3,202,660 (Zeile et al.) It is also useful for treating migraines as described in U.S. Patent No. 3,666,861 (Zaimis et al.) and for treating glaucoma as described in the literature references E. Edelhauser, V. Nemetz, Klin, Mbl. Augenheilkunde 160 (1972) 188 and R. Jahnke, H.W. Thumm, Klin. Mbl. Augenheilk. 161 (1972) 73. See also U.S. Patent Nos. 5,447,947 (Campbell) and 5,070,084 (Campbell) (treatment of sympathetic pain); 4,981,858 (Fisher et al.) and 5,106,831 (Fisher et al.) (treatment of senile dementia of the Alzheimer's type); 4,956,391 (Sapse) (treatment of symptoms of narcotics addiction, tinnitus and Alzheimer's disease); 4,949,848 (Tuttle et al.) (treatment of pruritus); U.S. Patent No. 4,788,189 (Glazer) (treatment of smoking withdrawal symptoms); Charney et al., 99:64150 CA, 1983 (anxiety); de Angelis, CA 123:1888417, 1995 (anxiety); Ramaswamy et al., CA 99:133603, 1983 (treatment of opiate addicts); Gold et al., CA 102:159846, 1984 (management of opiate withdrawal); Arnsten, et al., CA 117:62930, 1992 (treatment of Attention Deficit Disorder).

C. Pain Tracts And Central Nervous System Processing

The nerve tracts leading from the spinal cord to the lower brain areas, specifically the brainstem, begin operation at about the second month of gestation, continuing to develop for several months thereafter. Traumas occurring to the fetus and later newborn are registered and imprinted in these structures as well as certain limbic areas. As traumas, deprivation, lack of love and physical pain continue throughout childhood there

is a compounding of pain which is in part mediated by brainstem structures such as the pons, medulla, reticular activating system and locus ceruleus.

Thus, these brainstem structures "pump out" a constant energy flow as pain activates the system. Normally, the gating system of the central nervous system is adequate to block or "gate" the energy flow through the process of repression which is mediated by certain inhibitory neurotransmitters such as serotonin and GABA (gamma-amino-butyric acid). But as compounding of pain continues, a mother heavily depressed during pregnancy and taking drugs and alcohol, plus total neglect of the child in infancy, for example, the gating system becomes inadequate to the task. Because early trauma is reacted to by the highest level of nervous system available at the time of the trauma, there are specific symptoms to be expected, often those in the anatomic midline of the system, such as the stomach, lungs, and heart, with symptoms such as urination and diarrhea. These symptoms are mediated, then, by what is termed herein as "first-line" consciousness, which is also known as the "reptilian brain", as discussed by Paul Maclean of the National Institutes of Mental Health in his book, "The Triune Brain", published by University of Toronto Press in 1969.

D. Symptoms Mediated

The symptoms mediated on the brainstem level include sleep disturbances, bed wetting, heart palpitation, high blood pressure, sexual dysfunction such as premature ejaculation and frigidity, midline ailments such as colitis and gastritis, diarrhea and ulcers; and the psychological disorders include anxiety and depression, phobias and obsessive-compulsive disorders, hyperactivity, short attention span, lack of concentration, scattered

thoughts, attention deficit disorder, drug addiction; and this is not a totally inclusive list. Some forms of psychogenic epilepsy will also be the result of first-line disturbances; some epilepsy cases will respond to a first-line drug, namely, clonidine. The epilepsy cases which will respond are psychogenic because there is still a major psychological factor involved. Even when there is organic impairment in the brain, it is possible to heighten the seizure threshold by diminishing the level of neurologic impulses with which the brain has to deal.

Many people who cannot sit still and cannot concentrate long enough to read a book do not realize that they suffer from chronic low levels of anxiety deriving from first-line pain imprints which often begin with a traumatic birth process, including anoxia, strangulation by the cord, being stuck in the canal, unable to come out on time, and so forth. Thus, terror and low lying fear would be imprinted in the locus ceruleus which would then constantly drive electrical impulses innervating higher levels of brain function, ultimately affecting concentration and focus.

It is possible to list all of these symptoms separately but it must be kept in mind that they all emanate from deep brain structures that are involved in terror and pain and that the preferred medication pursuant to this invention is one that operates on lower brainstem levels, such as clonidine. Most of the symptoms are underlaid by these imprinted memories, which are not inert but carry a force, affecting, for example, amplitude and frequency of the brainwaves. See, Dr. Arthur Janov, "Why You Get Sick, How To Get Well," Dove Publishing, 1996. It is understood that all medical aspects of the treatment must be supervised by a licensed physician.

Detailed Description of Preferred Methods and Embodiments of the Invention

The principles of biology are remarkably similar among species and throughout evolution. How they are expressed differs but the principles remain, by and large, the same. For example, an amoeba in a benign environment who suddenly has india ink drops introduced into its petri dish incorporates the ink granules into its structure and then keeps them there in a vacuole until it finds itself in a salubrious environment, i.e., clean water. It then discharges these alien elements and goes on about its business.

This principle applies to humans. Alien forces in our environment that disturb our development, such as a drunken, threatening parent, can produce such terror as to cause a dislocation of normal functioning. What we do with these overwhelming feelings is sequester them in substructures of the brain, principally the limbic system and brain stem, and wait for a salubrious therapeutic environment to discharge the feelings and return to normal. In the meantime, the early event is imprinted and stored in subcortical structures waiting for release. This imprinted memory keeps the deformation process intact maintaining stress hormones at a high level and blood pressure in the hypertensive range, for example. The imprint constantly affects the alerting structures such as the locus ceruleus and the reticular activating system in the brain stem; and this keeps us activated, whether we know it or not. Mostly, we do not. But that is not the end of the story.

In order to understand what happens then a personal experience at the Pain Clinic of Johns Hopkins Hospital is now recounted. I went there because of long-standing chronic intense throat pain. They explained to me that it

might be "sympathetically maintained pain." What that means is that when there is damage to tissue, the nerve cells begin what is called "alpha sprouting". There is, in short, a proliferation of microscopic pain receptors which inform the system to be careful and not damage the tissue further through overuse. The pain receptors are part of a protective survival mechanism. Thereafter, in a feedback loop, the sympathetic nervous system activates the neurohormones, secreting noradrenalin which locks into the receptors and continues the pain. The pain, in turn activates the system toward protecting itself and survival. It is these internally produced catecholamines that ultimately affect the number and responsiveness of the alpha receptors.

Once there is severe physical damage, alpha receptors will sprout in the area of damage. I extrapolate from this, assuming that in the case of emotional damage, abandonment, neglect, lack of touch, the key pain-processing brainstem structures such as the locus ceruleus and medulla will undergo analogous processes. The hypothesis is that the system does not differentiate between physchological and physical insult. There are early traumas, even while being carried in the womb, that paint a fine line between physical and psychological damage. In fact, they are one and the same.

The principle of alpha sprouting is crucial here because when there is early birth trauma or serious early abandonment, the brain produces more alpha receptors, particularly in the locus ceruleus of the brain stem where it is likely that very early (birth, before and after) pain is registered; the locus ceruleus seems to be the terror center of the brain. Signals of fear are then sent to the upper level cortex which then assembles them into a

phobia, an obsession or anxiety, the origins of which for the person are rather recondite.

Why "anxiety", one might question? Because anxiety takes cortical processing, otherwise it is low level terror or fear. Anxiety is an "aware" state. We feel terrible, know something is wrong but do not know what or why. Emotional or psychological pain, which is always neurophysiologic, produces the same kind of pain receptors as physical tissue damage, and for the same reasons -- to guide us toward the avoidance of more damage and toward survival. Here is sympathetically maintained pain, no different than physical damage to tissue. This goes on and on until the pain is removed from lower centers, more precisely, when the pain is brought to conscious-awareness, making alpha 2 receptors superfluous. Feelings of anxiety no longer signal pain because the pain has been reacted to and becomes simply a memory. It has endured precisely because its tremendous valence prohibited it from entering conscious awareness for connection and integration. Thus pain reverberates throughout the limbic system and brain stem trying to find a way out. Once connected to higher levels, however, it is no longer an enduring pain; it is a memory shorn of its painful force. That is why at the end of one year of Primal Therapy the salivary cortisol levels of patients drop considerably. The system is under less stress.

Some key nerve tracts that carry pain signals from the spinal cord are in place, even before the development of the inhibitory neurotransmitter tracts such as the endorphine network, which becomes operational around the fourth month. Thus, if a carrying mother is left by her husband in the first few months of pregnancy, and suffers anxiety or depression, these can be transmitted to the fetus (through hormonal changes, among other factors)

which can register the trauma in the pain tracts of the brainstem and above. Hence, theoretically, it is possible that pain receptors make their appearance very early in gestation and can produce an underlying malaise which appears in infancy and childhood. In short, the newborn baby can be in pain whether he feels it, whether he is aware of it or not. And the same pain receptors which seem to underlie the symptoms of post traumatic stress syndrome in young children may already be at work before birth; the newborn who has previously undergone a severe trauma is in a post-traumatic state. It is these tracts and others that process the traumas just before and during birth, and it is these imprints affecting the brainstem and limbic areas that generate a lifetime of an excessive output of "nervous" energy. These early pains compounded with later childhood deprivations combine to produce an enormous amount of suppurating energy that causes attention deficit in children and adults, hyperactivity, distractibility, sleep disturbances and other afflictions that go on for a lifetime. Anand reports: "Nerve tracts carrying pain signals from the spinal cord to the lower centers of the brain are almost fully developed by 35-37 weeks." ("Growing Sensitive to Infant Pain," Insight, Feb 8, 1988, pages 52-53 referring to K.S. Anand.)

There is now a growing body of evidence for this position. The first sign that a receptor cell is present on the surface is that the cell has the ability to bind a specific substance, say, an inhibitory neurotransmitter such as serotonin or a facilitory transmitter such as dopamine. Some binding sites appear as early as 16-18 weeks after conception but most receptors are formed in the last three months. Rosengarten and Friedhoff have shown that altering the availability of a neurotransmitter during fetal development can change the

number of receptors later on. (Rosengarten, H., Friedman, E., Friedhoff, A.J., "Sensitive periods to the neuroleptic effect of haloperidol to reduce dopamine receptors." In A.M. Guiffrid-Stella, et al., "Nervous System Regeneration," Alan Liss, N.Y. 1983, pages 511-513.) So if you reduce the availability of dopamine at the receptor site prenatally (by blocking the developing receptor) there will be a much lower number of dopamine receptors after birth. That means that for a lifetime there will be insufficient dopamine activity; and that can mean that the level of cortical attention will be diminished by insufficient input proper for concentration and focus in the adult. If the prenatal alteration leads to up-regulation of the dopamine receptors and down regulation of serotonin receptors it may be that later there will be too much input from below with insufficient repression, again preventing focus and concentration.

Late research has found a correlation between lowered dopamine and depression. (See, Time, May 5, 1997, page 78.) Often, the investigators allude to genetic factors involved. It is my belief that most of us are not born with genetic deficits in dopamine. So much happens in utero, at birth and just after to account for alterations in dopamine setpoints. It is no accident that a hug or a kiss raises dopamine levels. Depression may be "caused" by genetically lowered dopamine, but it is more likely to be due to a bad uterine environment and then a bad, stifling, repressive home environment. Remember again, "love" enhances dopamine levels. There is late evidence, as well, of the role of dopamine in drug and alcohol addiction. It seems that the more the dopamine system is enhanced by drugs the more likely the addiction. Cocaine keeps dopamine levels high. Again, some of this can be traced to life in utero and soon

after birth. Dopamine plays a role in how well you sleep. In REM, dream sleep, levels of the repressive neurotransmitter serotonin, is much, much lower than usual. Without belaboring the point, all these problems may arise from traumas, slight as they may seem, in gestative life. And more, all these imprinted memories can be dampened, as we shall see, by certain chemicals delivered later on such as clonidine. Or, these memories can be relived, amorphous as they are, in terms of malaise, in our feeling therapy. One way we surmise about the altered setpoint of chemicals and neurotransmitters resulting from very early trauma is that such afflictions as hypothyroidism where the thyroid output is chronically low seem to normalize as a result of addressing and reliving early trauma.

Other investigators (Friedhoff, A.J., and J.C. Miller, "Prenatal neurotransmitter programming of postnatal receptor function," in Progress in Brain Research, Vol 73, 1988, G.J. Boer, et al., Elsivier Science Books) have found that there are "critical periods" during gestation when (and only when) permanent developmental changes could occur in the brains of experimental animals. Any deficit was never made up. There is every reason to think that this happens in humans. If the human mother is given heavy doses of tranquilizers (Haldol) during pregnancy, it may well permanently affect neurotransmitter levels in the fetus. And what that may mean is that the adult will never be "quite right"; may never have the wherewithal to repress properly. Hence the possibility of an attention deficit syndrome where all impulses impinge on the cortex at the same time. The adult is no longer able to properly repress the nonessential to focus on the essential. All input, in short, will have the same weight or importance.

With a dopamine alteration in the womb it may be that the child is hyperactive and becomes the one who can never sit still. So the speedy adult with little patience and a narrow window of tolerance and focus may be the result of what happened in the first weeks of pregnancy. All because of tranquilizers taken by the mother during pregnancy or perhaps too much coffee, alcohol and/or diet pills, etc (which contain "speed"). What haldol does is restrict the access of dopamine to the receptor; in this way quiets the individual. The effects of this are particularly evident in the emotional structures of the limbic system. (J. Engel, Per Lundborg, "Regional Changes in Monoamine Levels in the Rate of Tyrosine Hydroxylation in 4 Week Old Offspring of Nursing Mothers." Naunyn-Schmiedelberg, Arch. Pharmacol. 282, 327-334 (1974) Springer Verlag, page 333.) This has implications for later emotional behavior of the child and adult. The point of all this is that what may look like inherited problems can well be the result of an early environment of the fetus. We need to push back the envelope of social causes to the social/hormonal milieu of the developing fetus. What Friedhoff and Miller reiterate time and again is that prenatal drug exposure can have enduring changes in the system lasting a lifetime. Fetal exposure to antipsychotic drugs has occurred in children of psychotic women, and this in turn affects the sensitivity of receptor systems.

It may be that normal receptor development depends on exposure of these cells to dopamine. There have been a number of animal studies that show defective learning in the offspring of animal mothers given tranquilizers such as chlorpromazine (thorazine). The fetal environment during the first few weeks of womblife is critical, and later diseases may get their start in the subtle changes

which occur during this time. How well a child learns may depend significantly on what happened in the first twelve weeks of gestation.

If the carrying mother was very anxious while carrying, that anxiety is mediated by a number of hormone changes, which also affect the fetus for a lifetime, not the least of which are the stress hormones which have a decided effect on later sex hormone function. It is worth repeating what the authors above say: "By prenatal administration of pharmacological agents that alter transmitter supply to the emerging dopamine receptor, it has been found that receptor number (later) can be altered." (page 518) If this happens after birth the critical period is over and the animal will compensate by increasing the density of the receptors. But if it happens during pregnancy there is no commensurate compensation; and the result is lifelong behavioral change. More importantly, the authors state: "It is conceivable that maternal neuropeptides, maternal hormones (as a result of psychological states, my point) and maternally transmitted environmental chemicals could mediate such alterations." (page 518) What happens to the carrying mother counts a lot in later life. And the months of gestation seem to be more crucial than any other later social events. The brain is eminently malleable during this period, but after birth it seems to be set forevermore. What Friedhoff and Miller say is that, "From the adaptive standpoint, when a developing cell, bearing dopamine receptors, senses that there is little dopamine in its surroundings, it need express fewer receptors in order to match receptor number to transmitter supply." (page 519) It adapts to its environment so that when there is less supply there is

less physiological demand; one more homeostatic mechanism.

But it is not just cells we are discussing; they are part of a human being. And it is not just dopamine in question. It means that on every level this process can be taking place determining how we are formed and our later personality. The aim of homeostatic mechanisms is to keep the organism in balance. All is equilibrium. There can be a massive dislocation of function in the adult which arises out of the most minuscule events during gestation. Let us take this one step further.

Jean Lauder: "Neurotransmitters may be released from the tips of growing axons and sculpt the morphology of neighboring axons and target cells." ("Neurotransmitters as morphogens. Lauder, J. in G.J. Boer, Progress in Brain Research. Vol 73, cited above. page 365) During development, neurotransmitters, she says, can be considered morphogenetic signals, a function of their evolutionary history. They say, "change structure" to meet the new conditions or die! "You can't stay the same and expect to survive." A change in structure helps in the regulation of the transmitter. So we have a dialectical process: the alteration in neurotransmitters changes the structure of receiving cells and that in turn may alter the expression of neurotransmitters.

Since at the opening the point is made about biological principles remaining the same across and within species we might extrapolate from receptor formation in the fetus to what happens to the newborn who does not have close, warm, physical contact with the mother in the first few days or weeks of life. We note that there is a "critical period" or circumscribed window of opportunity. If the warmth comes later and not within that time frame it may come to naught; in the same way

that if you bandage an animal's eyes at birth for a specific period of months, and later remove the bandage the animal will never see again. If the need for love is not fulfilled early on when it is critical, it can never later be fulfilled by any means. You cannot love neurosis away. The only solution is to attack the central dynamics, the dialectical interplay between the forces of agitation by pain, and the forces of repression.

If we adopt the paradigm of receptor formation we may say that when no love is available very early on the system "shrinks" and does not develop a proper capacity for love. Remember that when the availability of a certain neurotransmitter is diminished in the fetus during gestation there will be fewer receptors for it. The body changes physiologically to meet new conditions. When the availability of love during the first months of life is diminished, the system will not develop the "love receptors" later on. That means that the capacity to receive and give love will be diminished for a lifetime.

One can have lots of hugs and kisses from the age of ten on, but that cannot fulfill the deprivation which occurred during the critical period just after birth. You cannot make up for that loss. You can attenuate it but no more than that.

With Primals, however, you can again feel the need during the critical period by returning to that time so that the need is no longer repressed. Originally, the need unfulfilled for a long period of time became painful and was necessarily repressed; that is how one loses touch with one's need. Failing the reliving, the best one can do is attenuate the pain. In the Garden Island study ("Children of Garden Island", Scientific American, April, 1989, pages 106-107) it was found that those children who suffered stress at birth could later be considered

adjusted if they had nurturing care ("a close bond with at least one caretaker") during their childhood. What we don't know is the internal toll of that adaptation and adjustment.

One can immediately counter this proposition by pointing out how well adjusted some orphans are even though spending the beginning months isolated in an institution. I would answer that external adjustment is not always a good index of how a person is inside. Early damage cannot be readily assessed with paper and pencil tests, particularly with the testing materials we have at hand today. Biologic markers are much more accurate: salivary cortisol levels, for example.

Feeling the need/pain normalizes the number of pain receptors as well as the destiny of the genetic code; my older male patients sometimes develop chest hair, for example, something that should have happened years before. These are microchanges as are the changes in pain receptor number and density as a result of intrauterine events. The placenta is not just a "barrier"; it is a gate which allows new elements to enter and alter development. The taking of tranquilizers by a carrying mother may alter the receptor capabilities in the fetus which in turn adjusts its later gene expression to conform to its early environment. If that environment is not propitious, the number of certain key pain and inhibitory receptors will diminish. Thus, it is assumed that this prenatal environment can later affect the reduction in inhibitory neurotransmitters so that the child and then the adult has difficulty repressing. The result of that is early colic or chronic anxiety. The early prenatal environment is different from the postbirth one. In the latter postbirth situation when certain elements are missing to form neurotransmitters

such as dopamine, the number of transmitters increases. Prenatal influences are turning out to be exceedingly important.

The locus ceruleus not only has a great concentration of noradrenaline receptors but also a dense concentration of opiate receptors. Events during pregnancy can alter the noradrenaline output and at the same time, in order to maintain balance, also stimulate the production of those quelling forces of opiate transmitters. Early imprints can achieve both. First, they galvanize the system to accommodate the pain (from say an anxious mother), and then provoke the system to suppress the pain when it reaches inordinate levels. Let us not forget that connecting fibers from the locus ceruleus reach down and up into and from the spinal cord at all levels. Pains in the first months after gestation can form a network between these structures. And, not surprisingly, noradrenaline output from the locus ceruleus affects the cerebral cortex, as mentioned causing up or down regulation of receptor density. Since the LC is related to fear and terror, those states will ultimately find their way into disrupting the work of the thinking, logical, perceiving cortex. Unsurprisingly, some drugs that work on anxiety (terror pushing upward) such as valium reduce the effects of LC stimulation. Hence, drugs that suppress LC such as clonidine may turn out to be the best anxiolytic agents. Researchers have found LC-NE fibers in the thalamus. Since the thalamus is like a central switchboard of the brain, relaying or blocking messages of emotion and pain to the cortex, these pathways are important.

A number of animal studies with pain (tail pinch or electrical stimulation) have found to affect the LC, both in terms of stimulation and inhibition. (see: "Nucleus

Locus Ceruleus: New Evidence of Anatomical and Physiological Specificity." S.L. Foote, et al., Physiological Reviews, Vol. 63, July 1983, page 868) Morphine reduces spontaneous LC-NE impulse activity. Clearly, the LC responds to pain.

The simple feeling of being overwhelmed can well begin with before-birth-imprints which already overload the system with high valence pain. These imprints, mediated by pain tracts which terminate in lower brain structures, are a source of constant innervation or "energy leaks". Thus, a current task in the present becomes "too much" for the person because it is compounded with perhaps fifth or six month trauma during gestation (an anxious mother fraught with worry over a sick husband). One might well say that there is no reason to feel so overwhelmed by so minor a task but the reason is there in an imprint which is overwhelming from an event engraved in the earliest months of life.

Associated with this feeling is what is known as Chronic Fatigue Syndrome. It is rather a complex symptom but one aspect is the fact that early imprints from birth and before require constant unconscious repression. The body is at work continuously to hold down these imprints, and this work is enormously tiring. What I have found with the use of clonidine in a few cases is that after the initial two days of fatigue from taking the medicine itself, afterward there is a great deal more energy in the person. The drug takes the place of the inhibitory networks in suppressing the pain and therefore liberates the person to deal with the world. One patient was able to do daily chores without the constant feeling that she had no energy to do anything. This was largely due to clonidine.

There are two main ways to deal with feelings of fatigue and being overwhelmed. One way is to suppress them with drugs that work on brainstem and limbic structure, which is solely a holding action, or, relive the traumas one by one, allowing them into conscious/awareness for final connection so that the energy source is finally dissipated.

The symptoms on this level dating from very early in life including fetal life are herein called, "first-line symptoms" (to be explained). These are not just any random symptoms but those associated with very early trauma when the highest level of neural organization was primitive and did not include a fully developed higher level neocortex. In short, we always react to trauma with the highest level neural organization available to us, and very early on, even in the womb, that would be brainstem and limbic system. And those levels mediate specific kinds of symptoms, from colitis to migraine, from hyperactivity to unfocused phobias.

There is already evidence that traumas in the earliest months of life change the neurobiology. (Ito, Y, Teicher, M.H., et al; "Increased Prevalence of Electrophysiological Abnormalities in Children with Psychological, Physical and Sexual Abuse," Journal of Neuropsychiatry, Vol 5, Number 4, Fall, 1993, pages 401-407.) These traumas can change the course of limbic system maturation; and, as Ito, Teicher, et al, point out, "may provide the biological substrate for a panoply of later psychiatric consequences, including affective instability, inability to modulate anger, poor impulse control, limited stress tolerance, episodic aggression, memory impairment and hallucinatory phenomena." (page 401) When one considers that the brain after a few weeks of post-birth development is basically the same as that

of a few weeks before birth, it is not surprising that traumas which occur in womb life can have everlasting effects, particularly on the emotional processing system. We just cannot see the trauma occurring. These authors point out (at page 401) that of 22 patients who were involved in incestuous relationships as a child, 77% had brainwave abnormalities.

Pain receptors seem to proliferate commensurate with the amount of trauma. The system enlarges its pain capacity to meet the extent of the damage, and for that it needs more receptors. Pain is the inevitable result of psychological damage. There is more: pain calls into existence more of its antagonist--the repressive receptors such as those for serotonin. Now, not only does the body expand its reactivity to pain but also its suppression of it. In evolution, being able to react sooner to danger or noxious stimuli was a survival trait. Being able to shut off pain and deal with the world was and is crucial.

Drugs that work on the brainstem (clonidine) also elevate the pre-serotonin inhibitor concentrations in the brainstem, thereby lessening the pain. (Pain brings into being what is needed to keep it from reaching conscious awareness, thus protecting consciousness from being overwhelmed and losing coherence. We block the overwhelming pain automatically through a system of gates that keeps imprinted memory in its lower storehouse. Paradoxically, if the pain suddenly bursts into conscious awareness there is real danger because heightened reactivity commensurate with the pain threatens survival. We have seen the vital signs rise when subjects have come close to early pain in therapy producing inordinate vital signs and brainwave patterns. It also happens to prepsychotics who enter our therapy where sudden early

pain arises without warning. Several hundred percent rises in brainwave amplitude is not unusual as is the tripling of heart rate and doubling of blood pressure. Postmortem studies of psychotics found increased dopamine receptors in the alerting structures of their brains. Pain is the most activating of stimuli as a mechanism of survival.

It is my belief that early imprinted pain is the central factor in the development of psychosis. In short, the brain "grows" the receptor it needs to handle stress and pain. Drugs that act to diminish dopamine transmission across the synapse also diminish the symptoms of psychosis. Current day tranquilizers help dampen any leakage of energy/tension/pain from lower brain centers. Some of them do so by interfering with the message of pain across nerve circuit synapses or junctions. (Many synaptic endings have autoreceptors that respond to transmitter release by presynaptic neurons. They serve a negative feedback function; when the presynaptic cell releases its transmitter some of it comes back to stimulate the autoreceptors, which then inhibit the cell from releasing more transmitter." Biological Psychiatry, J.W. Kalat, chapter 15, pages 422-423, Wadsworth Publishing Co., Belmont, Cal. 1988. Most antidepressant drugs decrease the sensitivity of the autoreceptors which ultimately allow for more transmitter release. Net effect: a decrease of the stimulation of the postsynaptic cell.)

For the past two decades we have focused on the serotonin and GABA receptors, those involved in repressing pain, without understanding that a dialectic process was under way in which pain receptors were proliferating as trauma provoked its antagonist into life. We had been looking at one side of the equation.

When citing serotonin research we might assume, although it is not yet confirmed, that alpha receptors increase in response to pain. We know, for example, that alpha 2 adrenergic receptors are increased in schizophrenia. (Pandey, Ghanshyam, N, et al, "Increased sup-3H-clonidine binding in the platelets of patients with depressive and schizophrenic disorders," Psychiatric Research, 1989, April, Vol. 28, pages 73-88) Having treated a number of psychotics I can attest to an enormous level of emotional pain in them. They have much more than one sees in neurotics, and their pain is much earlier in its origins. Many of my prepsychotics relive their birth or very early traumas in the first three weeks of therapy, which is almost never the case with "normal" neurotics who have a more intact defense system. The compounding of pain in psychotics makes for the leakage and the bubbling up of pain into conscious/awareness, so that they have to deal with pain every minute of their lives. They, therefore, never have a chance to construct an adequate defense apparatus, often developing bizarre ideation and hallucinations as a final defense against the onslaught of rising pain. They need external help, drugs and pain killers, to do so. The leakage of compounded imprinted pain is what accounts for a racing mind decades later when one is trying to concentrate or sleep; an event that seems arcane and mysterious to the sufferer. That is because it is all laid down so very early, long before cortical connections arrive to make sense out of it all.

How early the pain is laid down makes a considerable difference as to the amount of later damage to the organism. Recent research in animals has found that stress to a mother in late pregnancy resulted in increased serotonin receptors in the adult offspring.

(D. A. Peters, "Effects of Maternal Stress During Different Gestational Periods on the Serotonergic System in Adult Rat Offspring." . Pharmacology, Biochemistry and Behavior. 1989, Vol. 31, pgs 839-843.) Stress to a carrying mother, here, results in adverse effects in the brain of the offspring. This author, in the same journal of August 1987, states: "There is now a substantial body of evidence that exposure of pregnant animals can have long-lasting effects on the offspring." (page 669) This happens even with mild handling of the mother, a stressful event for the rat. What this and other research boils down to is that in animals (and presumably in humans based on our own experience), is that stress to a carrying mother can result in long lasting behavioral and systemic effects in the adult offspring.

Alpha 2 receptors can be stimulated by a medication called "clonidine." This stimulation or activation then results in the inhibition of the pain message. There is then the inhibition of the release of noradrenaline which attaches to the receptor to produce pain. The fact that clonidine both inhibits pain and lowers blood pressure should inform us that there is a relationship between pain and blood pressure; something we have seen for thirty years in patients who relive birth pains in which the blood pressure can reach very high levels. What clonidine does, inter alia, is block the release of noradrenaline from sympathetic terminals, preventing sympathetically maintained pain. It further acts like an opiate on the locus ceruleus, the storehouse of very early pains.

When clonidine is introduced into the system the number of alpha receptors in this and other areas involved in pain transmission is reduced. Recent

research on the locus ceruleus reveals that it is the fount of an enormous amount of stored pain energy which enervates the rest of the brain (and body). More important is that when stimulation reaches inordinate levels over time the locus ceruleus activation decreases.

This is one more way that high valence pain stimulation can be gated so that it does not reach conscious-awareness. It is a key protection for conscious awareness that it not be overly stimulated. Otherwise, the ability to function in the world is diminished, and there is an excessive heart rate and blood pressure. Even this diminished output by the locus ceruleus is only a palliative. There is still leakage of its diffuse energy in the absence of the exact connection. The leakage can be acted out in a myriad of ways throughout one's life, for example, rages, talking fast, hyperactivity, anxiety and panic attacks, etc., until the precise connection is made to the traumatic event; then, and only then, will it be resolved for good.

The locus ceruleus is comprised of very few neurons, only a few hundred to a few thousand, yet it sends its branches (axons) all over the brain. In this way it can activate the nervous system in a global way, and can do so long before we have words to describe it. It is no accident that the locus ceruleus has a very dense concentration of opiate receptors to squelch pain stimulation. (A substance mediating pain known as "substance P" increases LC activity.) Always the dialectic: the home of pain is also the home of pain suppression. Evolution seemed to "know" that wherever pain was organized its antagonist had to be manufactured, as well. To be more precise, morphine-like receptors are always found near the noradrenaline containing dendrites (the long thread-like "arms" emanating from the nerve

cell). Thus, stimulation/suppression form a dialectic unity. In any treatment, particularly psychotherapy, one must not treat only one side of the equation.

One person who is doing important work in the neurobiology of childhood trauma is Bruce D. Perry. He notes that the locus ceruleus plays a part in irritability, arousal, attention, and startle reaction. What he points out is something I have written about, namely, "It is likely that the functional capabilities of the central nervous system mediating stress in the adult are determined by the nature of the stress experiences during the development of these systems (in utero, during infancy and childhood)." ("Neurobiological Sequelae of Childhood Trauma: PTSD in Children", B.D. Perry, page 240. Found in: Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts: American Psychiatric Press, edited by M.M. Murburg, Wash. D.C.) What Perry is saying is that early trauma results in abnormal patterns of stress mediating neurotransmitters and hormones...and this will alter the catecholaminergic systems in the central nervous system.

I have hypothesized that those who have very early trauma have major disruptions in brain-stem organization and function. All this means poorly regulated brain-stem function. It also means poor control of the imprints of terror and pain as well as cardiovascular and other problems from an overactive sympathetic nervous system. He used clonidine on sexually abused children with good results. Perry suggests that alpha 2 receptors play a pivotal role in the signs and symptoms of post traumatic stress disorder in children (PTSD); again pointing to the universality of the proliferation of pain receptors as a result of either psychological or physical damage. The evidence from the research into

schizophrenia and Perry's work showing that psychological damage can be tempered by clonidine means that the human system does not distinguish between physical and psychological pain. It produces the pain receptors required irrespective of origin of the pain --social or physical. It needs reiterating: psychological pain as far as the human system is concerned is physical. It processes both in the same way and produces the kinds of pain receptors needed to accommodate the insult. More important, those receptors respond to the same medication, clonidine, as receptors sprouting as a result of physical tissue damage. There is no longer a need to separate the two. They are one and the same; only the origin is different.

What Schwartz and Perry have to say is that "[t]he locus ceruleus appears to be a central mediator of stress." (E. D. Schwartz, B.D. Perry, "The Post-Traumatic Response in Children and Adolescents," Psychiatric Clinics of North America, Vol 17, Number 2, June 1994, page 312). This bilateral structure, loaded with noradrenaline-containing neurons sends fibers to all major brain areas so that terror has access to the cortex, among other regions. When current stress resonates with and triggers off imprinted terror the whole body then can be involved in an anxiety attack. It is this system, connected as it is to the reticular activating system, that puts us on alert and makes us hypervigilant, sending such strong and diverse impulses upward that concentration is defeated. These same impulses can interfere with sleep and produce autonomic nervous system hyperactivity which may eventually result in ulcers and colitis. When my patients relive and resolve very early (birth and pre-birth) trauma there is a dramatic alleviation of the symptoms of colitis. It is

the deep brainstem imprint (along with limbic participation) stemming from very early trauma that is no doubt involved.

Perry has pointed out that alterations of the catecholamine output early in life, even in utero, can alter the development of the brain itself. (Perry, B., Placental and blood element neurotransmitter receptor regulation in humans": Progress in Brain Research, 73: 189-207, 1988.) Traumas after the second or third month of gestation can affect the migration of brain neurons, how they go to where they are supposed to go to form the neocortex, for example, as well as how and where the synapses develop. Late research shows that one of the limbic structures, the hippocampus, has found to be in disarray in the brains of autopsied psychotics. A recent study by Stephen Plotkin, University of California, Irvine, (reported in the Outlook, May 16, 1996: Study Links Schizophrenia, Cells) found that there is evidence of misplaced nerve cells in the brain. The author believes that it could be related to an early developmental brain process while still in the mother's womb. "It is an illness that begins during fetal development," he states. Thirty five percent of the schizophrenics studied (by autopsy) had evidence of abnormal nerve cells.

Another important study by Joyce Kovelman and Arnold Scheibel of the UCLA Brain Research Institute, on autopsied schizophrenics, found that the cells of the hippocampal region of the limbic system (the system that processes feelings) were in disarray, some rotated far from their usual position. The authors noted that the upside-down neurons were probably in place before birth and may "distort messages going to other parts of the

brain." (Kovelman, J. and Scheibel, A., "Biological Substrates of Schizophrenia," Currents, Sept. 1985.)

Another recent study seems to confirm our general hypothesis that something happens during pregnancy that leaves the baby vulnerable to later mental illness. University of California researchers found that the distribution of important brain cells known as "white matter neurons", is abnormal in adult schizophrenics. Dr. E.G. Jones has tied the cause to incidents in the second trimester of pregnancy. He concluded that psychotic brains have too many of these neurons. The result is lifelong faulty wiring of the brain. ("Scientists Link Faulty Distribution of Certain Brain Cells to Schizophrenia," L.A. Times, May 16, 1996, page B2.) When we use the expression "someone has his brains scrambled" to denote a mentally disturbed individual, we may not be far off the mark. What these traumas may do is leave their mark on several key brainstem structures such as the reticular activating system and the locus ceruleus, both loaded with norepinephrine, which thereafter are a continuous source of electrochemical output, more specifically of noradrenaline.

The evidence is accumulating -- traumas while being carried in the womb have a lifelong effect and can change brain function and structure permanently. One study is critical in all this. Lancet reported a study of blood samples taken from forty-six fetuses where the abdomen was punctured and a needle inserted into the liver. The fetuses responded with a 590% rise in stress hormone cortisol levels, and 183% rise in endorphin levels, the internally manufactured pain killer. It is clear that the fetus can respond to pain and can set in motion all the biochemical factors involved in pain and stress. It is also likely that these rises affect other hormones.

These enormous pains can be coded and stored for a lifetime affecting our behavior. (Salk, L. et al., "Relationship of Maternal and Perinatal Conditions to Eventual Adolescent Suicide," Lancet 1 1((1985):624-627)).

A trauma in the womb, as I have pointed out in my latest work, "Why You Get Sick," can change the set point for noradrenalin output for life making the person susceptible to lifelong tension, irritability, and hyperactivity (and hypermotility). While some stress is galvanizing and can aid adaptation, prolonged, inordinate stress can produce maladaptation: not for just the time of the trauma, but for a lifetime.

Perry's research demonstrates again and again that traumas such as the loss of a parent early in life alters the catecholamine output ("higher than controls", of circulating catecholamines). Interestingly, he found a high correlation between heart rate measures and alpha 2 receptor density; not surprising, says the author, because, "overall sympathetic tone is a major determinant of heart rate and platelet alpha 2 receptors." (ibid, page 8) Of the 34 children in his study, 85% had a resting heart rate of over 94 bpm. Thus, in a way, heart rate alone can be a good predictor of sympathetic output. In a feedback cycle the heart rate can feed back to the locus ceruleus and associated structures, and this in turn can again affect heart rate. And what do we find in anxiety states, post traumatic stress syndrome and general hyperactivity (with the inability to concentrate)?--a higher heart rate. In the psychotic and prepsychotic population there is also very high heart rate -- in his study, prior to clonidine treatment, their heart rate averaged 110. (ibid, page 10). Following four weeks of clonidine therapy the average was 98.

Clonidine may well be helpful for those who have cardiac problems.

The locus ceruleus is the main nucleus for noradrenaline secreting cells. Electrical stimulation of this structure produces severe anxiety, exactly what drug-withdrawal rebound does -- the need for calming drugs, i.e., clonidine. Clonidine is an excellent detox drug for its pain suppressing effects. This drug will prevent the need for pain-killing drugs, alcohol and cigarettes by suppressing the deep-lying pain that produces addiction, in the first place. If pain is artificially suppressed by drugs over time, the suppressed pain being held back for so long surges upward and requires even more suppression. Hence, methadone is given to heroin addicts in withdrawal. The sudden withdrawal of clonidine increases the output of noradrenaline, meaning, more pain and therefore more need to quell it; i.e., withdrawal syndrome. Clonidine may suppress seizure tendencies for those detoxing from heavy pain killers and/or alcohol.

In morphine withdrawal, as might be expected, there is more activity in the LC. The system is again in danger, and the LC is making the brain aware of it. One can reverse this firing pattern with clonidine and stop withdrawal symptoms. Clonidine slows the firing rate of LC neurons and also of the neurons in the medulla, another brain stem structure. This is of some importance because when my patients relive oxygen deprivation at birth they sometimes go into saw-tooth, raspy, locomotive, deep breathing, an event that can go on for twenty five minutes without hyperventilation syndrome. (Research carried out by my clinic and the UCLA pulmonary lab.) This type of breathing is largely organized by the medulla. Forced deep breathing comes from higher up and

leads automatically to a hyperventilation syndrome (tingly hands, dizziness and a tendency to pass out). In short, higher level deep breathing is a decision, a voluntary act which is organized much higher in the brain which is why it leads to hyperventilation syndrome. Anoxia and the need for oxygen remain as memory imprints low down in the brain and actually require the deep breathing. It is one more piece of evidence that leads us to believe that the imprint involves deep brain structures such as the locus ceruleus and medulla. Note: blocking pain (pain killing drugs) is calming. Enhancing pain does the opposite and is anxiety producing.

In another study by child psychiatrists, R.J. Harmon and Paula D. Riggs, with clonidine (patch) in five pre-school children with post traumatic stress syndrome found that there were improvements beyond what other therapies could achieve. (Journal of the American Academy of Child and Adolescent Psychiatry, Sept. 1996, pages 1247-1249). Aggressive behavior lessened in all of the children. Few episodes of impulsive behavior and emotional outbursts; there was less sleeplessness and nightmares, less disobedience and diminished anxiety. There were less side effects from the medication, and these children could then benefit from psychotherapy.

ANXIETY AND POST TRAUMATIC STRESS DISORDER

Clonidine has been shown to be effective in the treatment of panic disorders and anxiety, particularly as it relates to those with post-traumatic stress disorder. What is not clearly understood, however, is that many of us are in a chronic state of post-traumatic disorder only the precipitating events are no so clear. A child with a birth trauma, a child left in an incubator just after

birth, one who was neglected in the first months of life, who did not have loving attention, etc., are all post traumatic-stress cases. Because the trauma builds over time, it is not as dramatic as the Cambodians who lived in concentration camps and witnessed or underwent torture.

In short, many children are tortured psychologically early in life and are literally prisoners in their homes, obeying orders rigidly. All of the above deprivations produce later anxiety states and neuroses. A child who is constantly afraid of an abusive father lives in a permanent state of anxiety, recognized or not. That is why what is good for the post-traumatic stress case is good for many neuroses from phobias to obsessive compulsive disorders.

Rudolf Hoehn-Saric et al. found that clonidine helped patients become less anxious ("Effects of Clonidine on Anxiety Disorders, Arch. Gen. Psychiatry," Vol 38, Nov. 1981, pages 1278-79). What this study, and many others, neglect is the necessity for psychotherapy along with the drug; otherwise it makes little sense. Clearly, the drug is not a panacea but must be part of a general therapeutic armamentarium.

We would have to include obsessive compulsive disorders in this because the implication is that if a patient could not wash her hands 20 times a day she would be anxious. And one study found that OCD did respond well to clonidine. (John Knesevich, "Successful Treatment of Obsessive-Compulsive Disorder with Clonidine Hydrochloride," Am. J. Psychiatry, 139:3, March 1982, pages 364-369). A woman compelled to wash constantly during the day reported greater control over her thinking. She was later devoid of symptoms.

It is the early imprint that channels later adult experience and deforms perception and thought. Someone who spent a childhood terrified and unsafe later has to check the door locks many times a day "to feel safe." If the obsession-compulsion could not take place she would be faced with the terrifying feels of "unsafe and unprotected." It is a way to control those devastating feelings. We make our wives into mothers until finally they have had enough and leave, leaving us again without a mother as originally. We have not felt the pain of the full impact of not having a loving mother early on. A person goes on exhibiting himself in public until arrested because he has not felt and relived the early need for an emotional reaction in his parents who are generally emotional stones in these cases.

Repetitive behavior is based on unresolved feelings, and it is to those feelings we must look rather than the apparent surface behavior and ways to control those feelings. That is why we often get contradictory results with drugs. We are measuring the wrong thing -- we must not only address the acting-out behavior; we must investigate what drives that behavior. Ultimately, the drug works on those imprinted feelings discussed herein. (J.D. Kinzie, "Clonidine in Cambodian Patients with Posttraumatic Stress Disorder," J. of Nervous and Mental Disease, vol 177, No. 9, 1989, pages 546-548.) Kinzie, et al (just cited) has found improvement with clonidine in sleep disorders and traumatized patients. These patients were war casualties where the trauma was obvious. My point is that if we can look into a patient's past, as we do through the vehicle of reliving feelings where precise memory erupts, we can see equivalent traumas in the childhood of our patients. The difference is that in the ordinary garden variety neuroses the defense is fairly

well intact and memories well suppressed. In war veterans the defense system is shattered by current events, and repression is no longer viable.

The LC usually responds to incoming stimulation with large bursts of activity which then is followed by a quiescent period. It may well be that these bursts stimulated by low level imprints of pain may account for panic attacks in those who are not well defended. As noted above, there is a suppression of firing in the LC when the stimulation is too much, as it might be from high valence imprinted pain from a birth trauma: a trauma we have measured physiologically and through brainwaves. The exceptionally high readings attest to their power. What seems clear is that every biologic system has a shut-off switch to handle inordinate input. Clonidine activates the shut-off switch in the locus ceruleus.

What the two authors above (Schwartz and Perry) point out is something we have been aware of for some time: "Rats exposed to perinatal stress show major alterations in their stress response later in life." (page 313) In short, later adverse events in life resonate with the early imprinted trauma to produce inordinate, exacerbated reactions. What makes later events more traumatic is the stress and pain laid down very early on. For abused children the authors found later "frustration, anger, pain, helplessness, startle response, sleep abnormalities, impulsivity, sleep problems and altered cardiovascular regulation." (page 314)

What Perry found later was that stressed and abused children (physically abused, witnessed murder, etc.) responded well to clonidine which regulates the activity of the LC. ("Clonidine Decreases Symptoms of Physiological Hyperarousal in Traumatized Children,"

current submission to American Academy of Child and Adolescent Psychiatry, 2/17/96.) It helped those with attention deficit disorder. It improved sleep and helped stabilize heart function, slowed restlessness and decreased hypervigilance. Perry found that many of the impulse neuroses were improved with clonidine. This makes sense since non-verbal impulses predate ideation often used to hold back these forces. That is, very early pain becomes electrical impulses bereft of any ideas to rationalize and control them. There is another way to control these symptoms: allow the imprinted terror from the trauma to come into consciousness for integration, a small bit at a time, over months or years, obviating the need for drugs and suppression.

So why is it that clonidine can diminish an anxiety attack? Because pain is involved in anxiety, as is terror, a terror that trickles up to the cortex for processing as anxiety; or worse, if the compounding is severe, the cortex produces bizarre ideation as in paranoia, to "rationalize" the intrusion of the fright energy of the imprint. Anxiety is among other functions a warning signal. It portends of an input, now internal, (the imprint) that threatens the integrity of the brain system. When clonidine acts on pain receptors in the LC it turns off the firing neurons. And as expected, heightens the threshold for EEG arousal (as evoked by brainstem reticular stimulation), and diminishes anxiety. Not incidentally, clonidine seems to be effective in reducing migraine attacks. This is not surprising since it is my belief that many migraines derive from imprinted anoxia at birth, imprinted, in part, on the medulla and locus ceruleus.

Levels of Consciousness

In order to understand how and why clonidine works it will necessary to make a brief digression into the levels of consciousness; for it is my belief that very early trauma can and does reside (is imprinted) in brainstem structures in conjunction with the limbic system (the "feeling" brain). Very deep, early trauma can therefore account for a whole host of later symptoms emanating from these structures, including attention deficit disorder, aggressiveness, insomnia, sexual problems, migraine headaches, heart palpitation, high blood pressure, shortness of breath, anxiety and short attention span.

According to Paul Maclean of the Laboratory of Brain Evolution in Poolesville, Maryland, human beings have a "triune brain," made of up three elements: a reptilian brain, the (primarily) brainstem structures we share with reptiles; the paleomammalian brain, or limbic system, which we have in common with other mammals; and the mammalian brain, or neocortex. To account for what we have seen in Primal Therapy, I have taken this concept further. My discovery that Maclean's three brains are home to three distinct levels of consciousness has become a cornerstone of Primal theory. Diagnosis, prognosis, and access to feelings rely on this concept. Paul Maclean puts it as follows: "We are obliged to look at ourselves and the world through the eyes of three different mentalities -- two of which lack of power of speech. The human brain amounts to three interconnected biological computers, each with its own special intelligence, its own subjectivity, its own sense of time and space, its own memory, motor and other functions." (Maclean, Paul, The Triune Brain).

I agree with Maclean that these three levels of consciousness correspond to specific brain structures and

are intimately interconnected, though each level has different functions. What each of these three brains does and how they interact are fundamental to understanding neurosis.

The first brain level to evolve, which herein is called "first-line consciousness," is the instinctive level. Largely located in the brainstem and hypothalamus, it regulates vital functions.

The limbic system is the seat of the emotional "second-line consciousness," where our feelings reside. It is mediated by the brain's limbic system and temporal lobe.

On the "third line" or cortical level, we reason and develop ideas, integrating the input from the two lower levels, providing the meaning of experience.

The development of each level of consciousness mirrors the evolutionary development of our species. Just as hundreds of millions of years elapsed between the evolution of the first line and the arrival of the thinking cortex, a person's development of first-line consciousness far predates the time when his neo-cortex functions. This helps explain how we can experience trauma before we have words to describe what happened. And as shown herein, it helps explain how it is possible for us to be "unconscious" of memories which affect us for a lifetime.

Instinctual Consciousness

The first line involves the primitive nervous system. Although its structures are competent at birth, they actually begin processing during gestation and mediate the physiological changes in development. The first-line is the visceral mind, the caretaker of sensations, so that vital functions are largely under its

control: breathing, cardiovascular activity, hormone output, digestion and urinary processes, et al. First-line consciousness preserves homeostasis, meaning that it maintains our blood pressure, heart rate, and other vital functions at appropriate levels.

Since we always respond with the highest level of neurologic functioning available to us, traumas which occur before six months of age are likely to affect these functions. Hence, if a patient presents with colitis or palpitations, we may anticipate that a first-line trauma -- something which happened before the infant was six months old -- is involved. This may help to explain why some people have far lower pulse, blood pressure, and body temperature than others. We have seen that early trauma can change the set-point for the body's thermostat, hormones, and much of our biology, often playing an unseen but direct role in later physical illness. Because first-line development predates emotions, it cannot cry tears, as we see when repressed first-line traumas rise to consciousness. Nor, of course, can it speak, as language is a higher level function which comes later. When patients relive very early traumas, there are never any words involved. The first-line can, however, store the cataclysmic sensations of approaching death, the frenzied breathing and body movements, such as those which arise when traumatic birth memories break through the repressive barriers, as seen in the example described earlier. Moreover, these same memories, unseen but active physiologically, tax the organism for years and decades and can play a role in the development of cardiovascular disease and other ailments, as I shall explain later.

First-line Pains are the least accessible; it is the level from which memories are the most difficult to

retrieve. Perhaps because first-line feelings are so difficult to access, when they are accessed they are the most resolving of both symptoms and suffering and give rise to the most global insights. It is this level that is disrupted at the beginning of life altering hormone output, such as thyroid. And it is in reliving this level that hormone output is finally stabilized. We know that thyroxine (secreted by the thyroid gland) begins its manufacture at about twenty weeks of fetal age. Stress by the mother can be transmitted to the fetus making slight alterations in thyroxine set points. Later on, in childhood or adulthood one can see beginning tendencies to either oversecretion or undersecretion of thyroid hormones. Patients who were hypothyroid, listless and lacking energy, gaining weight too easily, are often no longer hypothyroid after reliving traumas on the first-line. Although patients make progress throughout their therapy, it is only when they access first-line that major biologic changes take place. Without access to this level, no one can imagine or believe what goes on here, and what an incredible impact trauma on the first-line has on later behavior and symptom development, how it shapes who we are and what we do. I shall show later on how we measure this level of functioning. But it is my opinion that clonidine may work on this level of functioning primarily.

Emotional Consciousness: How and Where We Process Feelings

The second line -- the "affective level" or "feeling mind" -- begins to develop at about the sixth month and continues into childhood. Over time, the infant relates to an ever-larger world than the breast and mother's cheek, establishing emotional attachments to parents;

siblings, aunts and uncles, pets, coding feelings on the second-line. This is the level of feeling states, emotional memories, tears, tics, and stuttering. It can be musical, develop images, and appreciate poetry. It is also where the strange images found in children's drawings come from and, later, in the paintings of artists.

The second-line cannot do calculus, but it can dream and mix emotions with first-line sensation to form the guts and agony of experience. It can defend consciousness against the terror of a first-line trauma and attenuate the force of low-lying imprinted memory by converting the terror into fearful dreams with monsters trying to strangle us, or to a phobia of enclosed places. The second-line encapsulates the sensations from the first-line. Under stress a child may develop a choking sensation. It is the first-line intruding on the second.

Anxiety is the result of a combination of deep bodily turbulence with non-specific third-line cortical arousal. That means that specific deep Pain stimulates the cortex in a diffuse way so that the person feels activated and agitated without knowing why. It feels bad, and we call it "anxiety." Once connected to real events and real scenes in the past it is no longer anxiety; it is consciously integrated deep memory.

A traumatic event such as incest which occurs at the age of four or five or six largely involves the second line. The suffering, feeling component of pain is stored on this level.

When our adult patients reliving an early second-line trauma begin to cry like an infant, indeed as an infant -- in a way that would be impossible if they tried to do so willfully -- it is a clear indication of the

fact that memories from different times of life reside on different levels of consciousness.

The Intellectual Level: How Thinking Defends Us Against Feeling and Why Being Smart Has Nothing to do With Neurosis

The third-line begins to play an active role at about age six and goes on developing until around age 20. Mediated by the brain's frontal lobe, the third-line organizes things intellectual. Third-line consciousness integrates the lower levels, helps inhibit impulses and feelings, deals with the external world, and provides the meaning of feelings.

Necessity is the mother of invention, especially in terms of brain function. A long time ago, when our ancestors had to hide from adversity the migration of brain cells upward and outward to form the neo-cortex gave them an evolutionary edge. Thanks to this evolutionary development we have inherited the ability to understand language and to speak. The neo-cortex deals in logic, rationality, concepts, calculation, and reality testing. It can develop ambition, plan for the future, have insights, be socially and politically aware and have a sense of time. It can be "reasonable," forgive, pretend, develop complex philosophies. The neo-cortex or third-line consciousness finds "reasons" to explain other people's behavior, enables us to project motives onto others, have faulty perceptions, and bend logic into accord with our internal truths.

Indeed, with the aid of a newly-developed cortex, we became able not only to escape from saber-toothed tigers and figure out where to find food and warmth, we also had a way to escape from our Pain-filled selves With third-

level consciousness we can think and solve problems, but we cannot feel without access to the second-line. The third-line conjures up ideas to defend against both second line and first-line trauma. The neo-cortex's ability to inhibit feeling permits us to focus, concentrate, make plans and set goals and follow them through, to keep functioning even though there may be a seething cauldron of Pain below. This survival mechanism allows many people who are very traumatized early in life to find a mystical deity as a way to shield themselves from Pain, not knowing that their beliefs are being generated by repressed material. It makes it possible for the same person to juxtapose complex scientific information with the most irrational ideas. One may be totally logical in working out a problem in differential calculus while simultaneously believing in an all-powerful being who created the world in six days; a brain surgeon can be a Moonie. Because it is shielded from the feelings stewing at a lower level of consciousness, the rational mind is useless to analyze the contradictions involved in the belief system. In fact, whatever else the neo-cortex does is an adjunct to this central function of repression. As we grow up, maturation of the greater cortical organization we develop brings with it greater capacity for repression.

Thus, we have three levels of consciousness, with each one separated by evolutionary time and serving specific functions in the psychic economy. On the first-line there are sensations but no tears or images; on the second-line, feelings and images but no complex ideas; on the third-line, complex thoughts but no feelings or sensations. Damage to one level will not necessarily affect another. For example, one can have the speech area of third-line consciousness damaged but still be

fully feeling. One can have one's motor functions impaired but retain crystal clear perception. Those in a coma are operating on the first-line, with the two higher levels inactive. They may continue to live for months or even years in a vegetative state. They make no contact and behave at a rudimentary level, certainly with no concept of what is going on -- but they are "functioning." Those who have woken from comas report that they perceived touch and reassurance at some level. Holding the hand of someone who is under anesthesia can help attenuate pain to some extent. The person still senses this contact even though he is "unconscious," or residing on another level of consciousness.

We can think of the first-line as a brain stem with a slight addition, very much like a shark brain. The brain of the turtle seems to have the first inchoate cortex in evolution allowing for second-line dream functioning. Finally, there is the brain of humans, combining these earlier brains with the new capacity for ideas and consciousness, or the ability to understand what might be going on down below.

Each level of consciousness contributes to what we call "mind." In a normal, healthy person, these three distinct minds function as a single mental apparatus, with fluid access between the levels. They work in harmony for the good of the organism, allowing the person to be a feeling, thinking being, with feeling and thinking integrated, with full reactivity so that she has healthy emotional reactions to outside stimuli and is able to think clearly about these emotions and use them as guides for behavior. Health means optimum coherence or connectedness among levels, harmonious functioning which serves survival.

But trauma interferes with this harmony, causing "unconsciousness." Repression interferes with integration among these three levels and causes a global dislocation of function in both the body and mind spheres. It makes organs oversecrete or undersecrete, warps the physical development and alters blood vessel function. With repression and neurosis we can feel one way and think another; behave one way and feel another; say one thing and mean another; not know what we are feeling; react in ways which are more linked to something that happened to us in the past than what is before us in the present. Why? We are reacting to the present through the filter of memories which are stored. These memories may and often do predate the words. The symptoms that we have in childhood and later on often drive from these early imprints. Anything that works to dampen the output of brainstem energy sources may ameliorate those symptoms.

Epileptic seizures are a case in point for first line damage. There is evidence from the work of Maclean (cited elsewhere) that often the epileptic seizure is forewarned by an aura, and this aura often includes feelings and sensations that I term first line: feelings of suffocation, doom, darkness, being overwhelmed, wanting someone nearby (from early isolation after birth), wanting to get "through it", etc. Most commonly some kind of terror is involved in the aura or warning. One epileptic put it this way: "it was different from any normal fear, inasmuch as it arose for no apparent reason, yet ... it had a peculiar familiarity as though I had previously experienced it." (Maclean page 439) I believe the patients have experienced it before unconsciously, and this event lowers the seizure threshold. It warns that an old terror is involved in the seizure. For that reason it may be that clonidine will attenuate such

problems. In another case history (page 442) a woman said, "I feel as though someone is going to smother me," seemingly straight out of the early birth trauma of suffocation. Other patients report feelings of sadness, "as if I want to cry." There are often suicidal ideas associated with the onset of epilepsy. The futility imprinted in a difficult birth or one with heavy doses of anesthetic immobilizing the newborn is often reported during the aura.

Interestingly, in a survey of hundreds of cases Maclean could find no aura dealing with the relationships with parents. This in my opinion is because that relationship is second line. It is largely first line inputs that play into epilepsy. It would seem that the central brain mechanisms involved are limbic system and connecting fibers to the brainstem.

It seems to be that if the hypothesis of lower level pain receptors proliferating as a result of early imprinted pain is true then the tranquilizer of choice would be clonidine, and in certain cases where cortical action needs to be stimulated in the service of enhanced repression, ritalin might be added. Thus, lower level pain would be diminished while the cortical forces inducing repression would be enhanced. In Primal lingo, clonidine is a first-line blocker and ritalin a third-line enhancer. Both aid repression. When given together the dose of each will need to be reduced.

Deprivation of need in rats, such as malnutrition in prenatal fetus results in increased concentration of NA in the brain at birth. The system, in short, is activated when there is deprivation of need, as, I submit, in the case of constant lack of parental love. This lack remains as an imprint putting the system on constant alert for a danger that is long past but ever

present in the brain. Clonidine given to these mothers during the malnutrition period prevented the excess secretion of NA and the symptoms ordinarily associated with malnutrition. Anxiety as a result of imprinted fear can be attenuated with clonidine which suppresses the terror output of the LC. The reticular activating system, which also is a major center for noradrenalin will be affected by clonidine. Clonidine, apparently, has important presynaptic action and inhibits the transmission of terror from the LC. It inhibits the NA transmission at the synapse. In brief, the terror cannot escape from its lower level structures, cannot insert itself into conscious awareness to make us overtly anxious.

The human system is exquisite in its logic. There is damage and it "grows" cells to handle it. When the cellular reaction is too great and threatens the organism there is a mechanism for further shut down. When that mechanism fails there are chemicals that aid in holding down pain so that the imprinted memory of trauma no longer feeds into the body producing heart palpitations and high blood pressure; nor does it insinuate itself into the cortex to produce a racing mind resulting in an inability to concentrate or sleep. In short, there are back up systems to handle overload. We need to have an overview of this elegant system and not hurry to tamper with it.

I have used the term "dialectic." Before we evoke a "higher intelligence" to describe the miracle of human development we should consider how the body and brain develop in response to outside stimuli. It constructs itself, so to speak out of the warp and woof of daily experience. Alpha 2 receptor proliferation is but one example of this process.

If any first-line symptom were pandemic to populations irrespective of class, it would be sleep disturbances. The mobilization against early pain is significant and keeps the mind racing as the person tries to fall asleep. This is particularly evident since the act of falling asleep is an accretion of attempts to quiet the mind and slip into unconsciousness -- the very unconscious that is agitated by early pain. Thus, the more one eases one's defenses in order to fall asleep the more one is in danger of deeper unconscious material. We found that the more our patients relieved very early imprinted trauma the better they slept. Otherwise, they are trapped by a continuous round of tranquilizers and sleeping pills.

THE RESEARCH PROJECT

We have embarked on a six week pilot study of the effects of clonidine on 26 of our patients each of whom has taken a "SCID", a nationally recognized test, to help in diagnosing individuals in accordance with the new diagnostic psychiatric manual. After diagnoses were made, and after one month to six weeks after beginning medication, we then gave each subject a test that I designed (see below). This test, in some respects, is aimed at Primal patients but is applicable to other individuals, as well. The results of this questionnaire were collated and is presented below.

Some of the results may seem paradoxical, as for example, that fact that a pill used for decades for high blood pressure can normalize those with low blood pressure. It is clear that it is never a simple matter of the dose of a drug or a diagnostic category. It matters what the internal environment is of those taking

the medicine. A brief digression to discuss that internal milieu.

The automatic functions of the system are governed by what is called the autonomic nervous system. Within this system are two subsystems working in harmony -- the sympathetic nervous system and the parasympathetic.

The sympathetic system directs energy-using behaviors such as the fight-or-flight response. It mobilizes us, raises body temperature, diminishes peripheral circulation (conserving blood for the muscles, preparing for fight or flight) so that the face is paler and the hands and feet may be cold. It makes us urinate frequently, sweat nervously, have a dry mouth and a higher voice.

By contrast, the parasympathetic branch controls energy-conserving processes; those of rest, sleep, and repair. It dilates the blood vessels, makes the skin warm, and promotes healing. When we are in a parasympathetic mode, with our musculature more relaxed to save energy, our voice lowers to a slow, mellifluous timbre.

A healthy person has a good balance between the two systems. Ideally, the two work together harmoniously, so that we are more "sympathetic" during the day and more "parasympathetic" during sleep, with a balanced mix of these two tendencies. But traumas which occur before we have seen the light of day can push us in one direction or the other. Because the early traumatic environment in the womb is imprinted into a fast developing neurophysiologic system, a system that can be warped by the mother's smoking, drinking, anxiety and depression, new input is absorbed and shaped by that matrix. (See "IMPRINTS" by the author for full discussion). In brief, the organism constantly responds to that early

environment and dislocates normal function as if that environment were a constant. The present contains the past so it is a constant.

Let us suppose that a carrying mother smokes and takes downers during her pregnancy. The fetal system may be rendered more passive than normal. Hormone output, such as thyroid, may accompany that passivity and be reduced. The dose of a tranquilizer which is enough to calm an adult enters the fetal system and overdoses it tremendously. It can produce a permanent dislocation of various functions; the stress hormone level may be elevated. Later, when any drug is given that mobilizes the system for whatever reason, it plays into an already activated, supercharged system. Conversely, if the system is heavily depressed during gestation, a depressive drug given to that adult later on may throw the system into a parasympathetic excess. A paradoxical reaction simply means that the system has not been accounted for in the prescription of medication. So there may be a reaction that is the opposite of what one would expect.

We are constantly reacting to a sequestered reality in real ways; viewed from the outside, however, that response seems unreal. Thus, high blood pressure is a real response to an early event. Artificially lowering that level with medication, for example, produces an unreal response, (a lower blood pressure) which seems real to outsiders. That is how ultimately we get sick, stricken down by our own reality. What is clear is that the human system keeps trying to right itself, to compensate for inordinate input, and the doctors keep trying to "unright" that self by forcing a truly abnormal reaction on the individual. Here is a truly paradoxical situation. The system consistently tries to put itself in harmony for survival by reacting appropriately (to an

internal reality), but that reaction itself can become life-threatening. Enter the treating physician who will help lower blood pressure. Now the person is caught; being appropriate or being alive.

A lot has to do with the birth trauma. In brief, when the neonate is born there is a "cut, print!" phenomenon going on which stamps in a general personality and physiological matrix. If the fetus was heavily drugged (if the mother is heavily anesthetized during birth) so that the system shuts down at the time of birth, the system may be skewed toward parasympathetic dominance. If the newborn is fighting to get out and is meeting one obstacle after another it may be that the "cut, print!" will sway the system into predominant sympathetic reactions. (All this is vastly oversimplified for purposes of discussion.) The reaction to birth is already somewhat shaped by what has already gone on in the first months of pregnancy. If the mother has smoked and taken downers and then is heavily anesthetized at birth, the chances for a passive baby (a passivity stamped in as a later personality tendency) are greatly enhanced.

Not everyone has been warped so that one branch predominates, but enough of us have been to make the concept valuable. Now let us insert into the adult parasympath with low blood pressure (remember it is this character who tends toward phlegmatism, passivity and low vital signs) some clonidine, normally designed to lower high blood pressure. But in this case the blood pressure rises because the very early pain which forced the individual to react prototypically in a parasympathetic manner has been suppressed. Because the trauma is repressed so is the prototypic reaction. The system is then free to respond normally for a time.

Not to move when the newborn is being strangled by the cord is a stamped in prototypic survival response, which, inter alia, dictates a lower blood pressure. But with the repression of that imprint the blood pressure, formerly pressed into service as part of a configuration of passive responses, can now rise temporarily.

Formerly, the parasympath was in the "give up" mode because giving up and not struggling meant survival. The paradoxical reaction is not so paradoxical once we understand the internal milieu. Reacting to the imprint produces an imbalance between the two subsystems; forcing the system to be skewed in favor of parasympathetic excess, in the case above. Clonidine inhibits the system from reacting to an overwhelming traumatic imprint, say, anoxia (lowered oxygen) at birth. The imprint is still there until integrated and resolved but the reactions have been blocked. The reactions which seem abnormal are actually appropriate responses to abnormally high valence input. So the medication suppresses the organism from reacting in tune with its inner environment. It separates out the inner reality from inner reactions. If the inner reality is ultimately not integrated the system will fall ill from blocked pain.

THE RESEARCH

Psychotherapeutic Treatment of Various Major DSM-IV Disorders With Transdermal Clonidine: A Preliminary Study

Twenty-One patients who met the criteria of DSM-IV: Diagnostic and Statistical Manual of

Mental Disorders for Anxiety and Mood Disorder symptoms completed a controlled study of clonidine administered transdermally in conjunction with an emotionally expressive psychotherapy. Most subjects felt that therapy had been improved. All subjects chose to continue taking clonidine. Larger, blinded studies of clonidine are indicated.

(Because patients are better able to tolerate transdermal clonidine (Weber et al., 1984) and because of the need for regulating multiple daily doses, we chose to study transdermal clonidine in the treatment of the various disorders of mental illness.)

As stated previously, early trauma, neglect and lack of love produce pain, a pain processed inter alia, by low brain systems and limbic structures. These pains occasion repression. We have always taken it as our task to ease repression and give natural feeling abilities back to suffering patients. Repressed early feelings do not disappear. (Janov et al., 1975). They remain trapped inside and build up a lasting tension and agitation throughout the body. This imprinted pain frequently brings on mood disorders and anxiety later in life. Helping a person to feel his hurts seems to unlock access to himself and thereby eases tension and anxiety.

The ability to express grief and feel pain, rather than repressing it has remarkable effects (Janov, 1996). Tension in the body diminishes (as measured by brain-wave patterns, electrophysiology and hormone studies: see Janov, The New Primal Scream) and psychosomatic symptoms are alleviated.

A substantial percentage of patients develop significant side effects from or do not respond to anti-anxiety medications and/or anti-depressants (insomnia, weight gain, impairment of motor activity, cognitive impairment, etc.). Some of these medications have multiple side effects and specific contraindications. There is a need for a medication that would have the following characteristics: (1) fewer side effects and a more consistent duration of action, (2) safe in patients of all ages and both genders, (3) safe in patients who are at risk for substance abuse, (4) improve patient acceptance and compliance, and (5) more effectively enhance therapeutic intervention, thereby allowing for improved access to repressed hurts.

Because clonidine reduces the frequency of firing cell bodies in the locus coeruleus and decreases release of norepinephrine (Starke and Altman, 1973) we would expect a less uncomfortable, less agitated, less restless state among those who take it. NE activity of the locus coeruleus as measured by implanted electrodes in unanesthetized cats increased during arousal from sleep to wakening and in response to the introduction of a novel stimulus (Aston-Jones and Bloom. 1981: Bloom, 1978: Foote and Bloom, 1979; Foote et al., 1980; Segal and Bloom. 1976). This NE activation increased arousal and external vigilance of the animal.

METHODS

Subjects

Nineteen adults with a mean age of $40^1/_2$ years and two children with a mean age of 7 years gave informed consent and were enrolled in the study. All subjects were Clonidine naive.

Structured Clinical Interview For DSM-IV Axis I Disorders (SCID) was administered to all patients to determine a DSM-IV diagnosis by David Lassoff, research associate. See Appendix A. (See Table 1). Terrance Jakubowski, Masters in Mathematics, Masters in Science Education and Ph.D (1998) in Research and Statistics did the statistical analysis using SPSS.

Table 1:

Column 1	Column 2	Column 3	Column 4	Column 5
Patients	Ages	Sex	Diagnosis	Independent Variable
#1	24	F	Anxiety Disorder	Clonidine
#2	31	F	Mood Disorder	Clonidine
#3	44	F	Anxiety Disorder	Clonidine
#4	27	F	Mood Disorder	Clonidine
#5	54	F	Mood Disorder	Clonidine
#6	08	F	Anxiety Disorder	Clonidine
#7	42	F	Anxiety Disorder	Clonidine
#8	50	F	Mood Disorder	Clonidine
#9	28	F	Anxiety Disorder	Clonidine
#10	55	F	Anxiety Disorder	Clonidine
#11	46	F	Mood Disorder	Clonidine
#12	52	F	Mood Disorder	Clonidine
#13	26	M	Mood Disorder	Clonidine
#14	32	M	Mood Disorder	Clonidine
#15	49	M	Anxiety Disorder	Clonidine
#16	47	M	Anxiety Disorder	Clonidine
#17	06	M	Anxiety Disorder	Clonidine
#18	38	M	Anxiety Disorder	Clonidine
#19	46	M	Mood Disorder	Clonidine
#20	45	M	Mood Disorder	Clonidine
#21	33	M	Mood Disorder	Clonidine

(Anxiety Disorders consist of DSM-IV criteria for Post Traumatic Stress Disorder, Panic Disorder, Generalized Anxiety Disorder, Anxiety Disorder NOS. Mood Disorders consist of DSM-IV criteria for Major Depressive Disorder, Dysthymic

Disorder, Cyclothymia, Bipolar I Disorder, Bipolar II Disorder, Depressive Disorder NOS)

Subjects were first monitored for various periods of time under psychotherapeutic clonidine-free conditions, except for two adult subjects who were treated with transdermal clonidine when they began psychotherapy. Doses were increased over the first month and then maintained for the remainder of the study period. The initial dose for both adults and children was 0.1 mg/day in the form of a single 3.5 cm patch, applied once a week. At the end of six weeks patients' psychotherapy were rated objectively by the psychotherapists they had been seeing before and during the time frame of the study with a rating questionnaire to elicit the therapists observations of the patients. The rating questionnaire was then given separately to the patients for their subjective responses.

At the end of the treatment period each subject completed a syndrome symptom questionnaire specifically designed for this research study to rate access to emotionality. This is a self-rated checklist that itemizes a variety of simple and complex physical and psychological symptoms, designed expressly for this research study to determine if the independent variable was either helpful or not helpful. Included in the scale was self-rated questions assessing mood, anger and sleep, an inventory assessing obsessional behavior, and questions used to evaluate a variety of neuropsychological characteristics.

At the end of the study, the subjects were asked which treatment period they thought had been the more

active, therapeutically. If they wanted to they could continue treatment with Clonidine.

Drug side effects were monitored and dosages were adjusted as needed.

Subgroups of patients who were not using Clonidine as outlined in the research protocols were analyzed separately. To determine the drug-specific effects, scores on the scale at the end of the treatment period were compared using a two-tailed paired t-test. Significance was defined at the 0.05 level.

Results

Twenty-one subjects completed the protocol. The frequency of response was assessed for a possible gender effect. When the rate of response was compared between males and females there was no significant difference between the two groups in how they reacted to the medication. Similarly, there was no apparent age effect on these results. The rate of response in various ages was not significantly different. Additionally, this sample included patients who had a history of treatment failure with other medications (tricyclic antidepressants, serotonin selective re-uptake inhibitors, benzodiazapines and/or anti-anxiety medications). One subject discontinued the study during the initial phase of medication treatment. Two subjects were dropped from the study due to not following the prescribed medical procedure.

The mean daily maintenance dose of Clonidine was 0.16 mg/day (dose range=0.1-0.3mg/day). All subjects started at 0.1 mg and dosages were adjusted. Correlation between dosage increase and access to the therapeutic

process was not shown to be statistically significant. However, access to the therapeutic process was shown to rise as dose was increased. The sample size of subjects who increased doses was too small and the amount of time that subjects were on the higher doses was too short to determine overall effect.

Based on the patients' opinion there was a significant effect of Clonidine on the therapeutic process with the probability of randomness measuring .001. Two patients had prior trials of anti-depressant medication that were discontinued due to either side effects or lack of response. Other medications that three patients were taking at the time of the study were monitored, and their use was not shown to be significant. However, caution must be noted because the sample size was very different. Significantly more patients did worse before the Clonidine than after, in their opinion.

Observational results from patients' therapists indicated that 8/13 (62%) of the patients were improving in their therapy, access to feeling as well as an increased level of comfort.

Table 2:

Key:

Responders: Patients that felt the medication was helpful.

Nonresponders: Patients that felt the medication was not helpful.

Comparison of Clonidine Response in the Treatment of Anxiety and Mood Disorder symptoms for more effective psychological intervention in an insight oriented, emotionally expressive therapy.

Group	Any Anxiety	Any Mood Disorders
N	10	11
Sex		
Male	4	5
Female	6	6
Mean Age		
All patients	34	40
Male	35	36.4
Female	33.5	43.3
Clinical Global Improvement (%)		
Responders	7 (70%)	7 (64%)
Nonresponders	3 (30%)	4 (36%)
Clinical Improvement; Resolving Therapy Sessions (Question #7)		
Responders	7 (70%)	3 (27%)
Nonresponders	3 (30%)	8 (73%)
Clinical Improvement; Feeling Better After Therapy Sessions (Question #8)		
Responders	6 (60%)	5 (45%)
Nonresponders	4 (40%)	6 (55%)

	OVERALL RATINGS	ANXIETY	MOOD DISORDERS

Questions

#1: (Access to feeling)

Responders	13 (62%)	7 (70%)	7 (64%)
Nonresponders	8 (38%)	3 (30%)	4 (36%)

Overall, patients felt the medication helped them with access to unconscious feelings. They could cry and emote easier and thereby could lift some of their repression.

#2: (Stop 1st line intrusion)

Responders	14 (67%)	6 (60%)	8 (73%)
Nonresponders	7 (33%)	4 (40%)	3 (27%)

This question is aimed at discovering how deep one's access goes. In sixty seven percent of the cases it went deeper than simply superficial crying.

#3 (Separate levels of consciousness)

Responders	15 (71%)	8 (80%)	7 (64%)
Nonresponders	6 (29%)	2 (20%)	4 (36%)

This question is a therapeutic one and indicates that the emotional level while on medication is available to the person.

Overall, the medication helped. Both groups responded positively with the anxiety group showing an 80% positive response rate.

#4 (Help therapeutic process)

Responders	17 (81%)	8 (80%)	9 (82%)
Nonresponders	4 (19%)	2 (20%)	2 (18%)

Both groups felt the therapeutic process was helped with an overall score of 81% responding positively. One of the more important statistics.

#5 (Irritability Question: Depressed patients in the mood disorder group who answered feeling "more" irritable were rated in the same "Responders" category as anxiety patients who answered feeling "less" irritable. Depressed patients, by and large, said they got more irritable, quicker, when under stress, but calmed down quicker.)

Responders	16 76%)	7 (70%)	9 (82%)
Nonresponders	5 (24%)	3 (30%)	2 (18%)

By and large, clonidine effectively diminishes irritability; the patients feel less agitated and "wound up", less explosive and out of control.

#6 (Connect to past)

Responders	13 (62%)	8 (80%)	5 (45%)
Nonresponders	8 (38%)	2 (20%)	6 (55%)

Part of having access to one's feelings is being able to relive past childhood trauma. Clonidine helped in this process.

#7 (Resolved after feeling session)

Responders	10 (48%)	7 (70%)	3 (27%)

Nonresponders	11 (52%)	3 (30%)	8 (73%)

Overall, positive response was less than half, 48%. The anxiety group showed a significant positive response of 70% in resolving and integrating feelings after clonidine. The Mood Disorder group showed only a 27% positive response.

#8 (How feeling after session)

Responders	11 (52%)	6 (60%)	5 (45%)
Nonresponders	10 (48%)	4 (40%)	6 (55%)

Overall, positive response was slightly better than half, 52%. The anxiety group responded more favorably (60%) than the Mood Disorder group, which responded less positively less than half the time.

#9 (Sensitive to crying)

Responders	10 (48%)	6 (60%)	4 (36%)
Nonresponders	11 (52%)	4 (40%)	7 (73%)

Overall, less than half responded favorably (48%). The Anxiety group responded positively 60%. The Mood Disorder group responded less than half at 36%. Clearly, in all categories it is the anxiety group that responds well to clonidine.

#10 (Impatience question: Same method of rating as in question #5)

Responders	13 (62%)	4 (40%)	9 (82%)
Nonreponders	8 (38%)	6 (60%)	2 (18%)

The anxiety group showed a 40% reduction in impatience (helpful), while the Mood Disorder group showed an even higher degree of impatience with clonidine.

#11 (Thinking and concentration)

Responders	15 (71%)	8 (80%)	7 (64%)
Nonresponders	6 (29%)	2 (20%)	4 (36%)

Overall positive response to the medication with a 71% increase in the ability to think and concentrate. Anxiety group = 80%. Mood Disorder group = 64%. The distractibility is helped significantly in both groups. Clonidine suppresses the eruption of impulses into the cortical areas.

#12 (How therapy is progressing)

Responders	13 (62%)	5 (50%)	7 (64%)
Nonresponders	8 (38%)	5 (50%)	4 (36%)

Overall positive response of 62%. Mood disorder group responded slightly better at 64%.

#13 (Getting along with others)

Responders	14 (67%)	7 (70%)	8 (73%)
Nonresponders	7 (33%)	3 (30%)	3 (27%)

Both groups responded more positive (67%). Anxiety group responded positive at 70% level. Mood disorder group responded positive at 73%.

#14 (Relaxed)

Responders	15 (71%)	7 (70%)	8 (73%)
Nonresponders	6 (29%)	3 (30%)	3 (27%)

Overall positive response of 71%. Anxiety group at 70% positive response, feeling more relaxed, which is the main aim in our frame of reference for the use of clonidine. Mood Disorder group responded positive at 73% level.

#15 (Sex life)			
Responders	10 (48%)	3 (33%)	7 (64%)
Nonresponders	11 (52%)	6 (67%)	4 (36%)

Little change in sex life with the drug, although two patients found it more difficult to get aroused and one patient with premature ejaculation found much better control.

#16 (Obsessing)			
Responders	17 (81%)	6 (67%)	10(91%)
Nonresponders	4 (19%)	3 (33%)	1(9%)

Overall, 81% less obsessing in our patient population with the medication. Anxiety group responded slightly better than half positive at 67%. Mood Disorder group responded with excellent response rate of 91% less obsessing.

#17 (Sleep)			
Responders	8 (38%)	4 (40%)	4 (36%)
Nonresponders	13 (62%)	6 (60%)	7 (64%)

We would have expected better sleep results because in individual cases there was improved sleep reported. The overall results, however, did not show it.

#18 (Overwhelmed)			
Responders	13 (62%)	6 (60%)	7 (64%)
Nonresponders	8 (38%)	4 (40%)	4 (36%)

A frequent finding is that patients on clonidine do often feel less overwhelmed. They no longer feel like in a haze with a "mountain on top of the head and they can't get out from under," as one put it.

#21 (Vital signs)			
Responders	8 (38%)	5 (56%)	4 (40%)
Nonresponders	13 (62%)	4 (44%)	6 (60%)

#22A (Intrusion in sessions)			
Responders	11 (52%)	4 (50%)	6 (60%)
Nonresponders	10 (48%)	4 (50%)	4 (40%)

Do feelings penetrate into conscious-awareness all of the time while in therapy? More said that they did not. However, the results were not terribly significant.

#22B (Intrusion in life)			
Responders	12 (57%)	4 (50%)	8 (80%)
Nonresponders	9 (43%)	4 (50%)	2(20%)

The same as above.

Patient Comments:

1. "Coping with day to day living is better...functioning is better...can get through the

day and overcome obstacles better...more relaxed around other people".

-A. B.

2. "I function better in daily life...less anxiety...less fearful...easier to talk to people...easier to complete projects."

-K. G.

3. "...I was taking .25mg of Xanax a day...after taking clonidine, it is mostly unneeded now...I can separate current anxiety from the past and I'm getting more relief...more resolution from feeling sessions."

-A. B.

4. "I have more desire for sex...orgasm is more potent...sensation is more acute...(in daily life) Feel there is more space in my head...clear headed...less diffused pain...can control outbursts better...generally feel better...have a lot less migraines"

-F.J.

5. "I love the ability (to now be able) to concentrate, to not feel overwhelmed all the time...I can do a variety of things efficiently and not be overwhelmed. I'm not anxious about socializing...I'm not physically so tense and contracted...I'm not (so) anxious...I just get things done (now)...I'm more available in the moment...feel happy and affectionate...enjoying my husband and daughter...not terribly put out by stuff that happens...not dredging up old wounds with every

slight...not so brittle or bristley...everything is simple...it's just what it is..."

-J. C.

6. "I can concentrate on what people are saying for longer periods of time and not be as bothered by anxiety when I am around other people."

-A. W.

7. "I can get along with less sleep (now)...I'm more patient...don't feel as overwhelmed...less panicky...less fear...less of feeling of not being able to cope."

-D. M.

8. "I have more clarity of thought..more reactive...not as overwhelmed, less suffering, (both) physical and psychological...(feel) less numb, less hopeless, less exhaustion...more of a sense of well-being.

-B. C.

9. "I feel more stable, calmer...not so frustrated with others, more patient...sleeping is less disturbed...anxiety has lessened...over excitability has gone down...fear and terror have lessened and I'm less irritable...I feel like the medication is the right thing for me...before, I didn't get enough relief during crisis situations, even when feeling...now there is some relief."

-R. L.

10. "I don't wake as frequently...sleep longer...fall asleep easier..."

-D. H.

11. "My brain seems to function better...concentration is stronger...don't jump around with thoughts as often...I don't struggle as long with a feeling...I'm more focused in the session, therefore I connect faster...I feel relieved, more physically relaxed, more centered altogether...I can somehow realize that I am feeling something about the past and not stay angry with the person in the present...I'm not presently having sex, but I have a desire, where before I really didn't...I don't sleep as sound...I have dreams that disturb me...nightmares...didn't have nightmares before.

-C. B.

12. "Don't have extreme anxiety (like before)...can relax...enjoy sex more...less tension headaches."

-S. N.

Question #19: <u>Other Symptoms Ameliorated</u>

anxiety
shorter periods of despair
headaches
urinary frequency
fear of people
generalized fear
migraine
terror
confusion
complacency
body aches
less hyper

depression

Question #20 Symptoms Not Improved

tension
anxiety
electricity in body
depression
loss of energy

Discussion

Only patients who took Clonidine were studied. There was no control group or cross-over treatment. Also, the length of time for the study (six weeks) was short. Although the study was designed to see if Clonidine would benefit patients who were having trouble with gaining access to emotions, patients did not all receive the same amount of psychotherapeutic treatment. Despite these limitations we were encouraged that twenty-one out of twenty-four subjects chose to continue transdermal clonidine with their psychotherapy after the study.

There was a positive response (7/10 & 7/11) noted in the sample (Table 2). However, the frequency of improvement in resolution in the anxiety group was significantly greater than the frequency of improvement in the mood disorder group (7/10 vs. 3/11).

Clonidine was an effective treatment for allowing access to the therapeutic process in very anxious patients. Seven out of ten (70%) anxiety disorder patients had more resolving therapy sessions with the adjunct of clonidine. Six out of ten (60%) patients with anxiety disorders reported feeling better after therapy sessions than before clonidine, while 4 (40%) patients

responded that they felt the same. No patients reported negative effects. However, clonidine was not shown to be as effective for mood disorder symptoms in gaining access to the therapeutic process. It is interesting to note that two subjects were taking a small amount of stimulant medication and a small amount of xanax with clonidine and reported positive responses to the questions of feeling more resolved and feeling better after therapy sessions (Table 2). While no statistical significance can be made from this small sample, a further study is indicated to determine clinical significance.

Clonidine appears to increase calmness and frustration tolerance as well as a sense of relaxation. This frequently results in better sleep patterns: ease of falling asleep and remaining asleep. A small dose of stimulant medication may help focus attention. This combination is safe and frequently permits a much lower dose of methylphenidate (MPH) than would be required if used alone (Hunt, 1987). It may be that a small dose of alprazolam in conjunction with clonidine and MPH may offer a combination that would be effective in both anxiety and mood disorder symptomology.

Treatment effects of 2.0mg-2.5mg of methylphenidate, 0.1mg-0.2mg of clonidine and 0.125mg-0.25mg of xanax in conjunction taken together would, it is hypothesized, help in severe anxiety cases. This would be an important follow-up study. Different combinations are indicated for study for efficacy value in different diagnostic categories. Data must be validated in double-blind fashion on a larger patient population, and with the use of a placebo. Further research is needed to document which clinical subtypes may respond preferentially to each medication, combination of medications and dosage levels. We have found that six weeks is not enough time

to properly evaluate results since doses must be adjusted regularly until the optimum is achieved for each patient. Responses are highly individual. For instance, we have found that those in great emotional pain must change patches every four to five days, and not the recommended one week as stated by the manufacturer. Starting at .1mg for one week usually is effective, moving upward to .15mg to .2mg within a week or two and remaining there. This is particularly true of those with panic attacks. Clonidine is particularly helpful, in our clinical experience, with panic cases.

In summary, patients we studied tolerated Clonidine well and most patients reported some degree of improvement and chose to continue long-term treatment. Some felt that for the first time in their adult lives they were anxiety free. Many were less irritable, less obsessing and driven. There was an overall feeling of relaxation. Patients, by and large, felt less overwhelmed and could concentrate and focus better. All of this makes sense when one considers that the generating sources of agitation and activation have been suppressed with the medication. We shall want to target groups such as epileptics, migraines, obsessives and attention deficit disorders in much larger numbers to see what results we obtain.

Significantly more patients did worse before the Clonidine than after, in their opinion. It is clear that those who are agitated and hypervigilant do best on clonidine since the vigilance center, the reticular activating system, along with the locus ceruleus, is one of the major loci for noradrenaline secreting cells. By and large, in my clinical experience, the anxious patient is one with a faulty gating system. Clonidine supports

gating by diminishing the assault of pain and stimulation on key structures and neurotransmitter networks.

In the second phase of the research, a double-blind control study with both a real patch and a false patch, for controls, will be used. We will then have two groups to study again using the SCID and where possible other objective measures, (if money permits) which will include salivary cortisol, EEG and electrophysiology over 3-6 months. See Appendix B.

As for controls, where possible, we would want to use those on our waiting list not in therapy and those in other therapies, to match against those on the medication who are in our therapy.

Thus, the first step taken so far was to see if the drug helps patients in the therapy and in what way. Secondly, we want to see if the drug helps those not in therapy, and with what afflictions and to what degree. As a result of the first study we know more about what to look for and what to measure. It has helped those few cases with ADD to concentrate and focus, to feel less distracted and scattered. We need to see many more of these kinds of cases to verify our preliminary findings. In my clinical experience, the ADDH responds very well to clonidine.

References

Aston-Jones, G. & Bloom, F.E. (1980), Impulse activity of locus coeruleus neurons in awake rats and squirrel

monkeys is a function of sensory stimulation and arousal. *Proc. Natl. Acad. Sci. U.S.A.*, 77:3033-3037.

Gold, M.S., Redmond, D.E. Jr., & Kleber, H.D. (1979), Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Amer. J. Psychiat.*, 136:100-102.

Hunt, Robert D., M.D. Treatment Effects of Oral and Transdermal Clonidine in Relation to Methylphenidate: An Open Pilot Study in ADD-H. *Psychopharmacology Bulletin* Vol. 23, No. 1, 1987: 111-114.

Janov, A., Holden, M., *Primal Man, The New Consciousness*, 1975, Thomas Y. Crowell Co., New York.

Janov, A., *Why You Get Sick, How You Get Well*, 1996, Dove Books, Los Angeles.

Manheim, P., Paalzow, L. & Hokfelt, B. (1982). Plasma clonidine in relation to blood pressure, catecholamines, and renin activity during long-term treatment of hypertension. *Clin. Pharmacol. Ther.*, 31:445-451.

Redmond, D.E., Jr. (1979), New and old evidence for the involvement of a brain norepinephrine system in anxiety. In: *Phenomenology and Treatment of Anxiety*, ed. W.E. Fann. A. Pokorny. I. Karacan & R. Williams. New York: Spectrum, pp. 153-203.

Starke, K. And Altman, K.P. Inhibition of adrenergic neurotransmission by clonidine: An action on prejunctal alpha-receptors. *Neuropharmacology* 12:339-349, 1973.

Starke, K., and Montel, H. Involvement of alpha-receptors in clonidine-induced inhibition of transmitter release from central monoamine neurons. *Neuropharmacology*, 12:1073-1080, 1973.

Weber MA, Drayer JIM: Clinical experience with rate controlled delivery of antihypertensive therapy by a transdermal system. Am Heart J 1984; 108:231-236.

In the later study objective measures will be used, as well, of the changes in patients: brainwaves, stress hormone levels (as measured by salivary cortisol) and vital sign levels. Since the usage of clonidine has gone on for decades it can be assumed that the dangers from the use of this drug are minimal and are outlined in the literature accompanying the drug distributed by Boehringer Ingelheim and Alza. There is ample literature to indicate where and how the drug works in the central nervous system. This drug has been used to good effect on very young children (five and six year olds), as well as adults. Anyone skilled in the art of medicine can apply clonidine to patients, given instructions by the manufacturer in the specific ways it should be done. If the physician were skilled in the use of this medication for a variety of ailments, high blood pressure, migraine and Alzheimer's disease, for example, he or she can use the art to the application of clonidine for uses as listed herein.

In terms of this double blind study a diminished amplitude in the alpha range and a lower frequency will be demonstrated, as well. In addition there will be a lowering of stress hormone levels as well as lower vital sign levels: slower heart rate, lower blood pressure and a

.5 to one degree (Fahrenheit) lowering of core body temperature. In contrast to controls there is expected to be a general calming, better concentration, far less anxiety and depression, enhanced focus on tasks at hand, greater tenacity in applying oneself to long range projects, stabilized sleep patterns with reduced nightmares and bad dreams, a reduction in obsessions and compulsions, less feelings of being driven, less tension and better control of impulses. There will also be a reduction in all first-line driven symptoms from migraines to colitis. These results are anticipated, not only from a group of non-psychotherapy subjects but also as distinguished from a group in conventional insight or behavioral therapy.

F. Hyperactivity, Attention Deficit Disorder, Short Attention Span And Poor Concentration

Hyperactivity, attention deficit disorder, short attention span and poor concentration mostly emanate, from leaky gates which allow low-level imprinted pain-energy to mount towards cortical conscious/awareness. We have already found in a pre-study of selected cases that clonidine is of substantial help. It stops the march of the terror-pain from reaching up into the areas which make us aware of suffering. (See Dr. Arthur Janov, "Why You Get Sick and How You Get Well", Dove Publishers, 1996 for a detailed discussion.) It is the upsurging imprinted memory force that ultimately disrupts cortical processes preventing concentration and focus. There is nothing as activating as pain, hence hyperactivity disorder would be expected from those with overactive brainstem structures. These structures are overactive due to their mediating very early (fetal life and for several months after birth) traumas.

Clonidine is the optimal tranquilizer because it works on the source of the problem, dampening the pain centers, preventing the pain from rising into awareness. Twenty-five years of research on blood pressure show a high correlation between blood pressure and pain. As the pain rises toward conscious-awareness in our therapy the temperature can mount three to four degrees in minutes, and the blood pressure may double in that time.

Example #1

In two cases of attention deficit disorder (ADD) using .2 clonidine patch for thirty days, one a man of forty-five, the other a woman of thirty-two who was thirty pounds overweight, both stated that they can now focus thoughts, have "space" in their brains to think and can "kick back" and concentrate without all the "noise" they usually have when trying to read, for example. The "noise" is all of the pain-imprinted impulses from below pushing upward, scrambling thoughts and producing incoherence and a state of confusion. The woman had previously undergone Behavior Therapy but without success.

Example #2

I asked a forty year old woman diagnosed as ADD to write me three lines to describe her condition. Somehow she could never get down to it despite three requests. Her husband described it as follows: "She can't stay focused. She can't cook -- too many ingredients overwhelms her; she can't pack for the same reason -- too many clothes. She can't start a project and finish it without many diversions -- watering the flowers, lighting a cigarette, checking her makeup, etc. She cannot carry anything through to the end. Yesterday she ate part of her meal, got up to do something, forgot that she was eating and

went about her day. She is easily distractible. After three weeks of clonidine she can pack, cook and actually get things done. It's amazing."

This is typical more or less of many individuals who are not diagnosed as ADD but suffer from it in some measure. What seems to happen is that the force from below constantly erupts into conscious/awareness bursting the coherence and continuity of the third-line. Each new eruption takes away attention from the task at hand and drives the person elsewhere. They follow the dictates of old pain/energy rather than the current event. By suppressing the originating source with clonidine there is far less eruption of pain into conscious/awareness and hence more concentration. These eruptions are not felt as pain; only as distractions. They force the focus elsewhere constantly. They prevent sleep by surging forth toward conscious/awareness propelling it to worry, obsess and imagine disasters. These are not thought disorders; they are disorders of feeling compelling thoughts into overdrive.

The bulk of research of ADD by others in the past has been on children. In contrast, the present invention is with adults. Clonidine administration pursuant to this invention is very effective in adults, particularly in those who are not diagnosed as ADD, but with subtle symptoms such as not being able to read a book or long article without feeling agitated. These patients have subtle lack of patience and inability to concentrate or focus on any task for any length of time; they are chronically confused and have too much agitation in their heads. It helps all these conditions for those not in

psychotherapy and who remain undiagnosed but who have these problems.

Example #3

Another case of a woman patient, unmarried, age twenty-six, who had to interrupt whatever she was working on to take a cigarette, make a phone call, take a walk, etc., found that after two weeks on clonidine that the hyperactive agitation slowed down so that none of those self-made interruptions was necessary. She could keep her mind on the task at hand. She had had an anoxic birth. The dose was a .2 patch.

The patch is used systematically so as to obtain an even dose without the sharp rises and falls occasioned by taking the pill. In all cases of adverse reaction the patch can be taken off immediately thus averting serious problems. Within one or two weeks a marked difference is seen, as evidenced by patient reports. There is a general slow-down of all activity, and those in Primal Therapy can focus on a single feeling, see it through until it is resolved and integrated on a cortical-thalamic level.

G. Insomnia, Sleep Interruption (Waking Up Several Times During Sleep)and Sleep Disorders

Patients who relive very early trauma, including the birth trauma, find that their insomnia disappears. These traumas make the mind race and prevent sleep. As the pain is integrated and resolved there is less cerebral agitation and sleep comes more easily. The racing mind is a mind racing away from the pain, a mind overly activated by the terror which is only partly gated from below. Clonidine helps suppress the upsurge of first-line traumatic memories during deep sleep which ordinarily interrupt continuous sleep. Deep sleep occurs on the

lower brain level first-line and is characterized by long, slow, deep brainwaves, the same kind of waves often seen just as a patient drops into the imminent reliving of a birth trauma.

Example #4

One patient, forty-eight years of age, had recurrent nightmares that woke her up several times each night. This had gone on most of her adult life. She would awaken in a terror state with her heart beating rapidly and reported that she was "out of breath." It was, she claimed, "the panic state where I was sure I was going to die." The .2 patch worn for five weeks radically diminished her nightmares so that she could have a relaxed sleep for the first time in years. Additionally, her husband noted that she thrashed a good deal less in her sleep. She remains on a .2 patch with no side effects. She claimed fatigue in the first two to three days; after that she had the same amount of energy as before. She also noticed a dry mouth for all of the time on clonidine.

Example #5

Six European individuals with serious sleep problems in an uncontrolled study (therefore anecdotal) were given .1 pills of clonidine. All reported enhanced sleep. Three of the individuals, all males, were in their twenties and from France. One female was forty years old and from England; the other two were Scandanavian, one woman was fifty-one and the other male was forty-six. After six weeks all wanted to continue with the pills. It seemed that one pill one hour before bedtime was sufficient to aid sleep. The individuals in this experiment were not given the name of the medicine until the end of the six weeks. None were patients but simply those who had

trouble falling asleep and staying asleep. One person who never had more than three hours straight sleep in his adult life found he could now sleep six straight hours. Clonidine seems to have been effective for sleep problems.

Example #6

A twenty-eight year old woman patient reported that from the age of eighteen on she had to masturbate every night in order to fall asleep. If she did not she was so filled with tension she could not fall asleep. With a .2 patch of clonidine taken for only one week she no longer had to masturbate and could sleep easily. She went on taking the patch until the present (12 weeks) and reports having no "falling asleep" problem.

Example #7

A thirty-two year old man told me that he could not remember when he ever had a full night's sleep. He would wake up after three hours of sleep, read for half an hour then take a sleep pill to fall back to sleep. With clonidine at .2 mg per day and after approximately thirty-five days, he reports knowing for the first time what a full night's sleep is. He also functions better because he is no longer exhausted during the day.

Clonidine will be an important sleeping pill (patch) not just for those who cannot fall asleep but for those who constantly wake up in anxiety states. It is in effect, the most important first-line, brainstem blocker extant. It can replace a host of sleeping pills; for example, the sleeping pill, Seconal is primarily a reticular activating system suppressant. Clonidine will "cap" the basic energy source of pain impulses.

H. Palpitations, Heart Problems Such As Angina, High Blood Pressure, Colitis, Ulcers

Here again, there is a lower brain, "first-line" midline nervous system activation leading to symptoms; the kind of symptoms that a newborn is capable of with its neocortex only partially developed. The lower brain centers are developed enough for gastric and heart reactions. Reliving and integrating the pain will reduce many of these symptoms. Clonidine will be helpful in these cases by slowing the innervation.

Example #8

One patient, forty-six years of age, who had periodic palpitations found them disappearing with the use of clonidine together with the process of Primal Therapy. Clonidine hastened the process of remission of symptoms which the psychotherapy would help eventually. The innervation of pain to the heart is diminished so that the heart muscle does not have to carry the burden of constant pain processing. Less angina attacks, are expected, as well. The .2 patch was sufficient here, but cases differ and the therapist or doctor will have to decide on optimum doses. Because first-line brainstem structures are highly connected to heart and lung function, it is expected that some heart problems will diminish with clonidine; a suppression of the excitation reduces the rapid heart beat while lowering blood pressure levels.

I. Anxiety, Panic Attacks, Phobias And Obsessive Compulsive Disorder

The origins of these symptoms are discussed in "The New Primal Scream," Enterprise Books, 1991. What seems to happen is that low level imprinted terror rises to conscious awareness when the person's defenses are

weakened. The source is still recondite but the fear arises and becomes known as anxiety, only because the source is hidden and mysterious. When patients relive the terror over months, bit by bit, the anxiety attacks diminish. One has a choice in suppressing these symptoms; either one pushes down the terror/pain with drugs such as clonidine, or one allows the pain to come up to conscious awareness for resolution. The latter requires substantial therapeutic skill. Clonidine helps the patient not be overwhelmed by feelings so that he or she can more easily integrate feelings. There is a choice of using the drug effectively without psychotherapy.

Example #9

One patient, a highly driven, forty year old businessman who had had chronic anxiety all of his adult life, never knew what it felt like to be anxiety free. Now he does. He started on .1 mg of clonidine and increased to .3. He is now steady at .2 patch for six weeks. A frequent comment by these kinds of patients is "[t]here is more rest and calm in my head." He found that alcohol and cigarettes were a help for his condition previously. He has no need for either since starting on clonidine, although he will have "an occasional glass of wine."

Example #10

Another patient, a thirty-eight year old teacher who suffered periodic panic attacks, found that the attacks were significantly reduced with clonidine. Again, the terror which might break through in a defenseless state is being held down by the drug. A .2 patch was used with an occasional .1 pill of clonidine in situations which were stressful. She had had conventional insight psychoanalytic therapy for two years previous without any

apparent benefit. She reported a dry mouth "as filled by cotton" throughout the test period of six weeks, which seems to be the case often with clonidine. She had taken Xanax for six months along with her previous therapy which did help somewhat, but not the effective way she claimed that clonidine helped her. She also found a rebound effect coming off Xanax which was quite uncomfortable and made her irritable, tense and unable to sleep well for a week.

Example #11

One case of a forty-four year old male musician with a phobia of elevators found that the phobia was diminished after one month of .1 patch of clonidine. Again, phobia is a displaced terror or fear which often begins its life with some terrifying event very early in life. His phobias were sporadic and only somewhat annoying. They did not ruin his life, and he did not feel he needed psychotherapy, but he was content to be able to enter an elevator again. He said that the phobia, specific to elevators, was highly annoying but he did not feel that he was neurotic in any way.

Example #12

One obsessive compulsive, thirty-five year old woman who had to check the locks in her house five to ten times a day began clonidine therapy two weeks ago. She is on a .1 patch and finds that she has less tendency to check the locks, although the tendency is still there. It is hypothesized that the pain/fear which drives the person to try to feel safe (feeling unsafe) is behind the symptom. The drug appears to be specific for this problem but also psychotherapy is recommended. She had undergone hypnotherapy for her problem which she said helped for

several weeks and then the symptoms came back in full force. She had been a Prozac user for the past three years which helped somewhat but has stopped so that clonidine's effects can be gauged.

J. Post-Traumatic Stress Syndrome

Post-traumatic stress syndrome has been written about extensively, particularly as a result of the Vietnam war where many soldiers seeing their buddies die, being under continuous assault, going days without sleep returned home tense, unable to sleep, with vivid nightmares, and were diagnosed as post traumatic stress syndrome. (See, Bury, J.S., "Pathology of War Neurosis," Lancet, 1: 97-99, 1918; also Blanchard E.B., "A Psycho-physiologic Study of Post Traumatic Stress Disorder in Vietnam Veterans," Psychiatric Quarterly, 54: 220-28, 1983.) It has been written about lately in regard to the effects of clonidine by Bruce Perry and associates in regard to very young children who had been abused, witnessed murder and underwent similar catastrophic experiences. (See, Perry, B., "Catecholamine Function in Post Traumatic Stress Disorder," American Psychiatric Press, Wash. D.C. 1994, pages 233-255.) He notes that PTSS is characterized by recurring intrusive recollection of the traumatic event, i.e., flashbacks, persistent symptoms of increased vigilance characterized by startled response, sleep difficulties, irritability, chronic hyperalert states, anxiety and hyperactivity. As noted elsewhere the children did very well on clonidine, leading Perry to believe that it is one major factor in the armamentarium of therapies.

There are traumas not so evident to fall into this classification, and that nearly every neurotic is in a post-traumatic stress syndrome. Traumas such as being

left in an incubator unattended for the first two months of life, neglect by unloving parents, watching parents' violence to each other (screaming and hitting), birth trauma such as anoxia or being strangled by the cord, and so on. One way we know this is that in studies with salivary cortisol done on my patients at St. Bartholomew's Hospital, London: patients with level levels of this stress hormone after eight months of therapy had significantly lower stress hormone levels. See "The New Primal Scream" by Dr. Arthur Janov. Psychophysiologic studies of vital signs, pursuant to this invention, found similar results. Part of this hypervigilance and hyperactivity involves the locus ceruleus plus other brainstem structures which galvanize the brain and physical system. Clonidine works on this so as to lower hyperactivity. It should read "hyperreactivity" since the body is responding to an imprinted trauma that is lodged in the neurologic system but is not palpable nor visible. Thus, clonidine is or can be a decisive factor in many neuroses.

As noted elsewhere in this disclosure, the seventeen children in the Perry study cited above were far less impulsive, less anxious, could concentrate better and were less hyperactive with clonidine. The prepsychotic children showed less symptoms; thus, pursuant to this invention it is an important drug not only for PTSS but for serious mental illness, as well.

Example #13

A forty-eight year old man, who was a veteran of the Vietnam War, had the classical PTSS including nightmares, flashbacks, anger episodes, often uncontrolled, general constant tension and irritability. Although he lost the flashbacks some five years ago, he still has the rest of

the symptoms. He was a medic who had seen soldiers dying. He also smoked marijuana continually and did fifteen LSD trips which totally unhinged his defense system. This assault on his defense system resulted in the memory of his father's suicide coming up. The death of the soldiers resonated with the memory of his father's suicide and together threw him into the post traumatic stress syndrome. He has been on a .2 mg. clonidine patch for four days. The clonidine will help bolster the gating system so that past memories will be held in check while he undergoes Primal Therapy therapy for one year. It will suppress his tension and irritability, as well.

K. Depression And Feeling Overwhelmed

In one of the eight published books by Dr. Arthur Janov there is a discussion of the origins of depression. In brief, depression, labored breathing, difficulty in moving, feeling heavy, without motivation or interest, futile and despairing often derives from an imprint surrounding birth where all those sensations were evident during the trauma (see Dr. Arthur Janov, "The New Primal Scream," Enterprise Publishers, 1991). Depression, then, is the subjective feeling of repression at work.

Anything that will ease the load of repression will help depression, hence the efficacy of an neuro-inhibitor such as Prozac. Clonidine is more effective because it works on the most significant imprints lodged and impressed low in the brain's neuraxis. Because much depression arises from very early traumas and deprivation (being left just after birth without closeness to the mother, for example), by suppressing part of the energy of the imprint psychotherapy will be much more effective. This is something which was already found in the six patients studied before the above-discussed Pilot Study

was in place. It makes integration of massive pains much easier because some of the force of those pains has been diminished by the medication. In figurative or symbolic terms, clonidine puts a "cap" on brainstem output so that the driving force is diminished. The same early imprinted forces that drive up blood pressure also innervate the cardiovascular system pushing the pulse faster and the stress hormone level higher.

Example #14

One thirty-eight year old woman who was heavily depressed most of her adult life has been on .2 patch for six weeks. She found that the drug significantly eased depression. She feels "light" for the first time, rather than feeling that she was carrying a big load around on her back. Her movements she said were no longer as though she were "wading through mud." It is anticipated to reduce the dose in the future to see if a lower sustaining dose can be effective. It is expected that a dose of .2 mg will be effective. She has been on antidepressants (librium, Elavil) for years with helpful results but not to the extent that clonidine has been able to help.

Enuresis (bed wetting) will be well controlled with the use of clonidine by dampening the explosive energy originating in the brainstem. Thus far, nearly all patients report the same phenomenon, namely, a feeling of not being so overwhelmed by the least little thing. What happens is that a current problem which ordinarily would resonate with a past deep-lying imprint to cause an overload of the neocortex no longer has the compounded power to overload it. When the past imprint is suppressed then the current task or problem is just what it is and does not carry with it a staggering load of pain, which,

to the person is not necessarily felt as pain; rather, it just all seemed "too much" in the words of one subject.

L. Drug, Alcohol And Cigarette Addiction

The reason that hard drugs tend to be addictive is that they quell so much of early unconscious pain, a pain that is not easy to see or measure; pains from difficult birth to the early lack of touch in the first months of life. The same can be said for alcohol addiction and cigarette smoking. As patients feel their early traumas, there is less tendency to abuse drugs or alcohol. It can be said that many current tranquilizers work on these pains, as well. Clonidine will significantly reduce the need for calming agents, whether cigarettes, alcohol, tranquilizers and hard drugs. Indeed, in some respects, clonidine works on some of the same centers that heroin does without the addictive aspects.

When heroin addicts were divided into two subgroups according to the presence or absence of morphine in bodily fluids, only the group with morphine showed decreases in alpha 2 adreonreceptors. See, Gabilondo, A.M., et al., "Mu opiod receptor and alpha 2 adrenoreceptor against binding sites in the post mortem brain of heroin addicts," Psychopharmacology, June 1994, 115, (1-2), 135-140. It is for this reason that heroin and other hard drugs are effective; they decrease the pain-mediating networks. Treatment using clonidine pursuant to this invention will do this without the addiction possibilities.

Example #15

A thirty year old woman who has been on Prozac for over two years for treatment of alcoholism was put on a .1 patch for two weeks with little results. The dose was raised to a .2 patch. She went off Prozac and felt no

need for it. She has been on clonidine for one month. It is expected that she will no longer need any of the usual tranquilizers. She had no previous psychotherapy and was under the care of a general practitioner.

We have given Clonidine to tobacco smokers who are not withdrawing and find a radically reduced need to smoke -- from three packs a day to five cigarettes a day. In another case a woman who had to have drinks after lunch and starting at five in the afternoon and on into the night found that she did not have to drink nearly as much and with no effort involved. In withdrawal there is a rebound effect from suddenly withdrawing from heavy drugs or alcohol and the pain that was suppressed before suddenly surges upward into the classical withdrawal syndrome, e.g., shakes, headaches, dizziness, nausea, unclear thinking and weakness. A steady amount of drugs, cigarettes or alcohol keeps all this under control but stopping suddenly puts the system into a shock situation. In contrast, Clonidine holds down the agitation caused by suppressed pain and lessens the need to repress. When taken daily it attenuates the agitation factor and hence lessens the need to hold back the tension and anxiety associated with it. Pain is the most mobilizing factor for the human system as it galvanizes the system to combat this nocuous input. Further specific examples of using clonidine pursuant to this invention to treat addictions follow.

Example #16

A thirty year old man, a smoker since the age of 13, was smoking two packs a day minimum. He had a cough which was getting worse, had tried Schick Behavioral Therapy where they showed him piles of ashes and cigarette butts

in the most disgusting presentation possible, but nothing helped. He was put on clonidine .1 pills twice a day for two weeks, then three times a day for eight weeks. He was able to cut down to ten cigarettes per day effortlessly. He said that he rarely even thought about smoking except that at times it was an automatic reflex which led him to light up. With continued use of clonidine he should be able to give up smoking.

Example #17

A forty-two year old obese woman, a compulsive eater, who had tried any number of diet programs from Jenny Craig on, is currently on Weight Watchers where she has to weigh in frequently. She claims that the shame helps but she can only cut down slightly and then only for a short time. We tried her on a .2 clonidine patch for ten weeks. She was able to cut down on her eating without effort and lost 15 pounds over the ten weeks. She feels optimistic about this program. She claimed fatigue for the first three days on the medication but afterwards she said she had no further symptoms. We will continue with the program with her and anticipate a continual loss of weight.

Example #18

A twenty-five year old New Zealand woman who is a Primal patient and was a heavy drinker (almost a fifth of gin a day and a heavy drinker since she was seventeen) was having trouble cutting down in the initial stages of the therapy. We started a program of .1 patch of clonidine and built up to .3 over four weeks. She claimed that it helped her cut down her drinking so that she could take advantage of the therapy. She said it was as though she lost her need to drink and it happened without her trying or willing. We plan to continue the program and build to

.4 over time if she can accept such a dose. It is now 11 weeks later and she is still off drink.

Example #19

This is a twenty-eight year old heroin addict whom we accept only on the provision that he stop the drugs once he started Primal Therapy. He had tried almost every therapy imaginable from psychoanalysis to behavior therapy to drying out clinics and sleep therapy where he was put out from almost three days. The latter he claimed helped for a week or two. He felt relaxed and had no need for drugs for several days after the sleep therapy but it did not last. We tried him on .1 clonidine pills twice per day for two weeks and then three times per day for eight weeks. After the eighth week he could manage only on vicodin three times per day in small doses without the need for heroin. He was a serious case who had forged prescriptions and was threatened with jail when he came to us. He believes that the pills plus the reliving therapy have helped him immensely. We shall continue with the program.

M. Severe Mental Illness -- Psychosis And Borderline Neurosis And Epilepsy

According to a report in New Scientist (27, Sept. 1997) citing the work of Edward Reynolds of King's College, University of London, the world's most common neurologic disorder is epilepsy -- one hundred million people will suffer from it at one time in their lives; forty million at any given time. It is truly a world-wide affliction. Part of this is accounted for by birth-related difficulties. Three quarters of the afflicted persons in the world receive no treatment at all. It

would appear that the simplest kind of treatment for some individuals would be clonidine. Because the drug works on the locus ceruleus, which is also one key structure implicated in seizures it is hypothesized that it could be the drug of choice; it is also easy to administer.

It is important to attenuate the epileptic seizures because the predominant attitude about them is that the person is mentally ill. In some countries such as India and China there are laws against them marrying. In England one of the lowest amounts for any kind of research was apportioned for epilepsy, far behind cancer and AIDS.

Example #20

A .2 patch is used on a twenty-two year old girl who was delusional. She imagines someone in Europe is sending messages through the television to have someone cut off her breasts. Clonidine will diminish the delusion.

Example #21

A fifty-nine year old man sees blood everywhere -- on his shoes, on the wall, etc. Clonidine treatment has just begun, and it is expected that these hallucinations will consequently diminish.

Clonidine will be an important adjunct for the treatments of the two above patients inasmuch as over the years most psychotics are heavily burdened by very early first-line pain; and the literature, as quoted in "Why You Get Sick," by Dr. Arthur Janov, confirms this hypothesis. Research is heavily weighted toward very early traumas in psychotics and borderline cases. See pages 119-124, pages 30-39. See also Andreasen, N.C. et al, "Thalamic Abnormalities in Schizophrenia Visualized Through Magnetic Resonance Imaging," Science News. (1980): 279; Alkon,

Daniel, "Memory's Voice," Harper Collins, N.Y. 1992, pg. 159; Anand, K.J.S., "Halothane-Morphine Compared with High-Dose Sufentanil for Anesthesia and Postoperative Analgesia in Neonatal Cardiac Surgery," New England J. of Medicine, 326 (1992): 1-9; and Davis, J., "The Effects of Hypoxia on Brain Neurotransmitter Systems," Advances in Neurology, 26 (1979): 219-223. The thrust of low-lying pain/energy in those who are weakly defended upsets cortical cohesion forcing the person to concoct ideas that are out of keeping with current reality but much in keeping with past imprinted reality. It is expected that suppressing that past reality will render the delusion unnecessary.

Epilepsy occurs for many reasons; generally it is a random, massive discharge of nerve impulses over all the brain, often originating in the temporal lobe. The brain may be vulnerable because of a lesion or other abnormalities. Clonidine will diminish the amount of latent, overpowering nervous energy so as to attenuate the strength and frequency of an attack; in brief, it will raise the seizure threshold.

Example #22

One man in his twenties and another in his thirties, both with epilepsy, are each given a sustaining dose of clonidine (.2 mg. via patch) together with dilantin (10 mg.). There will be a reduction, if not elimination, of the epileptic attacks so long as they continue on the medication and adjust the dosage accordingly. It is also imperative that a reliving therapy, e.g. Primal Therapy, accompany the use of the medication to eliminate the generating source of the attack; that is, to heighten the threshold so that even when there are physical brain vulnerabilities, a seizure is less likely. Dilantin will

stabilize the cells, in conjunction with clonidine to suppress the reticular activating system and locus ceruleus activating sources.

N. Impulse Neuroses, Which Includes Rage Attacks, Compulsive Masturbation, Acting Without Reflecting

The constant output of pain-energy from traumas which occurred before or during birth, long before we have the cortical capacity to reason, inhibit and control our impulses, is one main cause of impulsive acting out. The fetus and newborn are a mass of raw impulses. Those impulses are electrical phenomena which will drive later behavior before the neocortex is adequate to the task of repression. There are many studies showing that prisoners have a history of birth difficulties (See "Imprints," Dr. Arthur Janov, 1983). Thus, it is necessary to examine the drug's affect on those being released from prison, e.g., those who are considered impulse neurotics, exhibitionists, voyeurs and rapists. Those subjects will have better self control once the heavy load of electrical first-line impulses are suppressed by clonidine.

By implication, those being released from mental institutions may also benefit from the drug, which will help their post-hospital social adjustment. It must be assumed that imprinted rage becomes out of control as the amount of overall energy driving it is increased. And conversely, to suppress the overarching energy of early deprivation of love, of violent parents beating a helpless child will bring back control to those who have been chronically angry and rageful. Everything has been tried on these kinds of cases from surgery to certain limbic structures to the serotonin enhancing drugs such as Prozac

with limited results. It is not simply the rage centers in specific centers of the hypothalamus plus other rage centers in other limbic structures that must be addressed. The powerful global energy source in the brainstem which innervates those limbic nuclei must be held back, as well. Clonidine will accomplish this.

O. Sexual Dysfunction, Frigidity And Premature Ejaculation

Clonidine may have a paradoxical effect on individuals. A normal person may find the libido diminished as well as it being more difficult to achieve an orgasm. One needs a high level of energy output for that. On the other hand, clonidine may suppress enough energy output so that premature ejaculation is avoided. Thus, during a high level of excitement there will be less compounding of pain-fear-energy of original traumatic imprints so as to diminish a forceful uncontrolled ejaculation. Some of the first-line energy, in short, that would overwhelm the control possibilities of the person will be suppressed by the drug thus aiding control.

In the case of frigidity the dampening of pain imprints will occasion less repression (via inhibitory neurotransmiters) so that under sexual excitement the woman will be able to achieve higher levels of excitement without the usual shutdown.

Example #23

A forty year old woman reports being freer in sex but that she comes to orgasm only after a much longer time of stimulation. The general level of excitement is less due to the clonidine. She has been using a .1 patch with an occasional .1 mg pill every other day for six weeks. This woman had sexual counseling before for one year, to no

avail. She now reports that sex "seems less painful than before."

LIPOSOMAL DELIVERY SYSTEMS

A liposome is a bilayered shell made from lipids (fatty substances) and has found particular usage in medicine because it acts as an artificial cell. A lipid has a water-soluble component and a water-insoluble component, the latter of which causes the lipids to form a bilayer which folds in on itself (creating the shell) to avoid water. This shell formation entraps any water-soluble drugs in the interior, thus protecting the drug from attack once the liposome enters the body while simultaneously making the drug less toxic and more target-specific. Liposomes are microscopic (1/50th the width of human hair), lecithin spherical vesicles that form an "oil" membrane bubble surrounding the active ingredients within the formula. They act as a carrier to penetrate porous membranes and deliver the active ingredient directly to the bloodstream within seconds.

Recently, liposomes have been evaluated as delivery systems for drugs, vitamins and cosmetic materials. Companies use liposomes as carriers for lipophilic (lipid-liking) drugs such as anti-tumor drugs, anti-cancer drugs and anti-fungal drugs. They have become an important model in fundamental biomembrane research, including biophysical, biochemical, and cell biological studies of membrane and cell function. They are thoroughly studied in several applications, including drug delivery systems in medical applications and as controlled release systems. Liposomes can be custom designed for almost any need by varying the lipid content, size, surface charge, and method of preparation. There are laboratories that can

design and manufacture liposomes in a multitude of formats to suit specific delivery requirements.

A special quality of liposomes is that they enable water soluble and water insoluble materials to be used together when necessary. Benefits of liposomal technology include:

- Controlled Delivery Systems
- Greater Bioavailability
- Biodegradable, Non-Toxic
- Increased Absorption, Greater Concentration in Submucosal Layer for Prolonged Release
- Decreased Dosage
- No Binders, Fillers, Dyes, Glues, etc.
- Higher Concentration in Bloodstream
- Carry Both Water and Oil Soluble Payloads
- Prevention of Oxidation
- Can Solubilize Recalcitrant Compounds
- Protein Stabilization
- Pure High Quality Ingredients
- Faster Results
- No Barriers to Overcome (Some people have a hard time swallowing pills)

Liposomes were first proposed and tested as a drug delivery system 25 years ago. Advances in our understanding of the fate and behavior of liposomes at the cellular and subcellular level in vivo have allowed the rational design of constructs for the use in the treatment and prevention of disease, both in experimental animals and clinically (Gregoriadis G., 1995). Liposomes have found widespread use as model membrane systems, and have been extensively investigated for their potential as drug

carriers. Initially, there was widespread enthusiasm for the use of liposomal drug carriers, but this waned as they failed to live up to expectations for all but a few, limited cases.

Liposomal drug-delivery systems have come of age in recent years, with several liposomal drugs currently in advanced clinical trials or already on the market. Liposomes have been adopted by numerous researchers as the vehicle of choice for drug delivery and targeting. Allen, T.M. and Chonn, A. (1987) FEBS Lett. 223, 42-46; Torchillin, V.P. (1985) Crit. Rev. Ther. Drug Carrier Syst. 2, 65-115; Gregoriadis, G., ed. (1988) Liposomes as Carriers of Drugs: Recent Trends and Progress, Wiley; Puisieux, F., Couvreur, P., Delattre, J. and Devissagnet, J-P., eds (1995) Liposomes: New Systems and new Trends in their Applications, Editions de Sante. Extensive studies on the behavior of liposomes and its control within the biological environment, as well as great leaps in liposome technology (Gregoriadis, G., ed. (1993) Liposome Technology (Vols I-III, 2nd edn), CRC Press) have recently culminated in the development of several licensed for use in humans.

It is clear from numerous pre-clinical and clinical studies that drugs, such as anti-tumor drugs, packaged in liposomes exhibit reduced toxicities, while retaining, or gaining enhanced efficacy. This results, in part, from altered pharmacokinetics, which lead to drug accumulation at disease sites, such as tumors, and reduced distribution to sensitive tissues. Fusogenic liposomal systems that are under development have the potential to deliver drugs intracellularly, and this is expected to markedly enhance therapeutic activity. To facilitate their association with any fixed cells that are anatomically accessible to the carrier, liposomes must be able to recognize target

cells, bind to them and, if necessary, penetrate their interior. The idea of using cell-specific ligands attached to the vesicle surface as a means of promoting cell recognition by liposomes was put forward, and demonstrated to be feasible, twenty years ago. Gregoriadis, G., Neerunjun, D. and Hunt, R.(1977) Life Sci. 21, 357-370; Gregoriadis, G. and Neerunjun, D. (1975) Biochem. Biopphys. Res. Commun. 65, 537-544. Advances in liposome design are leading to new applications for the delivery of new biotechnology products, such as recombinant proteins, antisense oligonucleotides and cloned genes (Chonn A. et al., 1995). Liposome drug delivery systems are being developed for a variety of drugs (Vemuri S, et al., 1995).

To date, the story of liposomes as drug-delivery systems appears to be a success. It has come about as a result of the accumulated knowledge of their interaction with in vivo systems, which has allowed for the rational design of vesicle constructs, and through the sophisticated advances in liposome technology (Gregoriadis, G., (1995) Trends in Biotechnology 13 (12):527-537). However, research is ongoing and there are challenges for other applications still to be made.

In regard to liposomal delivery of clonidine. It is particularly advantageous for afflictions such as migraine and epilepsy where there is sometimes an aura or prodromal warning of the coming attack. If clonidine is taken and absorbed within a short period of time after the warning, it may be possible to attenuate or eliminate the attack. It is helpful if the migraine, for example, is attenuated before the full symptom is established.

We would expect the dosage to be the same as with other delivery systems but further research and experimentation will be needed to establish optimum doses.

The preferable delivery system here would be a nasal spray for immediate access to physiologic processes.

DISCUSSION

The success in the future of the treatment will be measured by the SCID (structured interview, paper and pencil) and later by objective measures of cortisol, psychophysiology and brainwaves, if possible. Brainmapping has been in use by us for some three years now (as reported in "Why You Get Sick and How You Get Well," Dr. Arthur Janov, 1996). For the double blind study it is planned to have an equal number of males and females, between the ages of 23 and 55. To reiterate, because clonidine works on lower brain systems it is the most effective tranquilizer and antidepressant that exists, as disclosed herein.

Pursuant to the present invention a clonidine patch (plus pills when necessary) will accomplish the following:

1. Lessen or eliminate anxiety and panic attacks, with a recommended dose of .2 to .3 patch. The patient will know what the optimal dose is because the symptoms will be lessened within three to four weeks. In conjunction with Primal Therapy it will hasten the ability of the patient to reach deep levels of consciousness without being overwhelmed by a deluge of compounded infancy and childhood traumatic memories. If the anxiety attacks are sporadic then the minimal sustaining dose of .2 patch can be used. If they are acute and constant then a .3 patch may be used until the symptoms are abated. As an option, but not always necessary, it can be used in conjunction with a minimal dose of ritalin (10 mg.). Ritalin works on the thalamus and upward through the

dopamine system thus enhancing cortical-thalamic gating, making cortical repressive function more effective. Thus in each case where ritalin may help as an adjunct to clonidine it is understood that ritalin is a third-line neocortical enhancer, while clonidine is a first-line brainstem suppressant. For severe cases, as judged by a physician and therapist, a combination of the two medications in a single or dual patch or single pill will be effective. Examples of constructions of specific preferred single or dual patches are 10 mg. of Ritalin combined in a pill with .1 clonidine. Although a clonidine patch together with a ritalin pill is preferred, a clonidine-ritalin patch can be used. Alternatively, a lower dose of both together can be taken, after clonidine by itself has been tried. In this way the imprint is held down while any excess leakage of pain-energy is suppressed by a well-functioning repressive cortex. The result is a calming effect where the person feels relaxed without tension and agitation.

2. Will diminish or eliminate short attention span, inability to focus and difficulty with coherent thoughts. A dose of between .3 and .4 patch can be used, and also can be used in conjunction with a minimal dose of ritalin. When ritalin is used then minimal doses of clonidine and ritalin are called for. There is a synergistic effect producing a relaxed brain.

3. Diminish or eliminate being awakened several times during the night by rising memory imprints which produce nightmares and bad dreams, while the person is in a relatively defenseless state.

4. Will diminish or eliminate premature ejaculation, frigidity and other sexual dysfunctions including the impulses neuroses of exhibitionist, voyeurism and rape. It will also diminish neurotic compulsive masturbation (as a way of reducing the amount of excess energy/tension in the system) and other compulsive sexual impulses.

5. Will diminish or eliminate addictions and obsessive compulsive disorders as well as specific phobias from fear of elevators to fear of going out of the house. This drug will diminish or dampen the fear and terror centers of the neuraxis.

6. Will diminish or stop depression, manic depression and the constant feeling of being overwhelmed by suppressing the deep-lying imprints of which the person is totally unconscious.

7. Will aid immeasurably in the control of severe mental disturbance including psychosis and borderline cases by allowing the cortex is develop cohesion without the constant interruption and disruption by low lying traumatic imprints. Clonidine can suppress excess energy from reaching cortical centers where the force is converted into delusions. The hypothesis is that paranoid ideation will be lessened.

8. Will diminish symptoms of certain heart conditions, such as palpitations, by dampening the innervation to the heart of energy producing impulses occasioned by early traumatic imprints. Angina should also succumb to the treatment by clonidine. The

constriction against pain is the usual biologic reaction, and that would include heart muscles.

9. Will diminish or eliminate the symptoms of colitis and ulcers and other midline ailments or afflictions including shortness of breath and inability to catch one's breath.

10. Will diminish the strength and frequency of epileptic attacks, and other kinds of seizures-like symptoms; for example, it will help the symptoms of stuttering. A patch of .2 to .4 mg. clonidine will be helpful, but the dose will have to be determined empirically.

11. Will diminish or eliminate some eating disorders and addictions such as overeating, inasmuch as overeaters often are trying to stuff back pain and fear with food. The only other drug that blocks first-line effectively is heroin. Clonidine can affect those same lower structures without the addictive probabilities. A .3 patch or more initially is called for in addictive cases, not just for detox but to replace the need for hard drugs.

12. Will diminish or eliminate violent tendencies, temper tantrums and uncontrolled aggression.

13. As an adjunct to Primal Therapy and other psychotherapies to keep the patient from being overwhelmed by inordinate feelings; to help in integration of painful memories from the past.

14. Will diminish or eliminate many afflictions by starting with a .1 mg patch for two days. If there are no

adverse effects, the .1 mg patch is replaced with a .2 mg patch. If the symptom persists and is severe, i.e. psychosis, a .3 or even a .4 mg. patch can be used wherein the patch is taken off every six to seven days.

15. Will diminish or eliminate post traumatic stress syndrome.

The thrust of our current research is that patients sleep better and sounder, there is much less of a racing mind, they are not feeling overwhelmed by the least new element in their lives (particularly when this resonates with first-line traumas that together produce the feeling of being overwhelmed), there is "space" in the brain to allow new input, to think and reflect and to solve problems without a whole lot of extraneous input. Subjects claim they do not have to deal with pain every minute of the day.

Previously it is reported that it took so much energy to read a paragraph because they had to read it three times before it would sink in (characteristic of the ADD syndrome). They feel more readily on the feeling level without contamination of first-line input, and they resolve feelings during a session without feeling rotten afterwards (due to dredging up of first-line associated pain). Feelings are shorter and cleaner. It may well be that clonidine is used up when patients are in deep pain. This drug holds promise for those not in therapy, as well; who suffer from first-line symptoms, anxiety, distractibility, racing mind, depression, ADD, and insomnia.

From the foregoing detailed description, it will be evident that there are a number of changes, adaptations and modifications of the present invention which come

within the province of those skilled in the art. However, it is intended that all such variations not departing from the spirit of the invention be considered as within the scope thereof.

APPENDIX A

QUESTIONNAIRE FOR CLONIDINE SUBJECTS

1. Does the drug give more or less access to feeling?
more.....
less.....

2. Does the drug stop first-line intrustion?
yes.....
no.....

3. Does the drug separate the levels of consciousness?
yes.....
no.....

4. Does the drug help the therapeutic process?
yes.....
no.....

5. Do you feel more or less irritable?
more.....
less.....

6. Do you find it easier or more difficult to connect to your past?
easier.....
more difficult.....

7. Do you feel more or less resolved after a feeling session?
more.....
less.....

8. Do you feel better, worse or the same after a feeling session?
better.....
worse.....
explain.....

9. Are you more or less sensitive to crying with the drug?
more.....
less.....

10. Do you feel more or less impatient with the drug?
more.....
less.....

11. Do you find it easier to think and concentrate with the drug?
yes.....
no.....
why?.....

12. Is the therapy going faster or slower with the drug?
faster.....
slower....
explain.....

13. Are you getting along better or worse with others?
better....
worse....
in what way?.....

14. Are you more or less relaxed with the use of the drug?
less....

more.....

15. Has your sex life gotten better or worse?
Better.....
Worse.....
In what way?...

16. Are you obsessing more or less?
More....
Less.....

17. Are you sleeping better or worse?
better.....
worse.....
In what way?.....

18. Do you feel more or less overwhelmed?
more....
less.....
Do you know why?.....

19. Please list the symptoms, both physical and psychological, that have been ameliorated as a result of taking the drug.
A
B
C
D
E
F

20. Please list those symptoms not improved.

A

B

C

21. Have vital signs gone up or down after clonidine?

22. Intrusion (e.g., coughing):

a. more or less in sessions?

b. more or less in life?

Othér comments.....

APPENDIX B

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semistructered interview for making the major DSM-IV Axis I diagnoses. It was designed to increase diagnostic validity by helping to facilitate the application of diagnostic criteria of the DSM-IV and by systematically probing for symptoms that might otherwise be overlooked.

The SCID-CV (Clinical Version) covers only those DSM-IV diagnoses most commonly seen in clinical practice and excludes most of the subtypes and specifiers.

For most of the disorders in the SCID-CV, the full diagnostic criteria are included (with corresponding interview questions). However, some disorders are included in the SCID-CV in a summarized format in which a brief description of the disorder is provided in lieu of the full criteria.

The Clinical Version of the SCID was used to measure a suspected DSM-IV diagnosis. For example, upon hearing a patient describe what appears to be Post Traumatic Stress Disorder (PTSD), the PTSD module of the SCID-CV can be used to inquire about the specific DSM-IV criteria for PTSD.

In this instance it provides actual DSM-IV criteria and questions for PTSD in order to obtain information necessary to judge the diagnostic criteria.

The SCID-CV is divided into six modules, however they are not completely self-contained. Although the modules are intended to be administered in sequence, the order may be changed under certain conditions. For example, the module for alcohol use disorder may be used before other modules if the patient is presenting with the appropriate symptoms.

Although specific structured questions are provided to help elicit diagnostic information, it is important to understand that the ratings on the SCID-CV are judgments about the diagnostic criteria and not necessarily the patient's answers to the questions. More often than not, an unelaborated "yes" or "no" answer is not enough information to determine whether a criterion is met. It is usually necessary to ask the patient to elaborate or provide specific examples. If convinced that a particular symptom is present, the patient's denial of the symptom should not go unchallenged. For each disorder, there is the indication whether it is "current" (i.e., if the full criteria have ever been met at any time during the current month), and/or "lifetime" (if the full criteria have ever been met during the patient's life).

Although it was developed to produce a more efficient and more reliable instrument for accurate diagnosis of symptoms, the SCID does not provide any criteria for rating ranges of emotionality, depths of feelings, or one's access to feelings. It does not provide diagnostic criteria on determining which neurological levels the disturbance(s) originated, thereby severely limiting the formulation of a valid treatment plan. Since mental illness is heavily intertwined with emotional responses, the SCID can only be a partial diagnostic tool that covers categories of symptomatic behavior rather than indicating deep lying pain...).

What is Claimed is:

1. A method of treating a condition or affliction selected from the group of sleep disorders, epilepsy and drug, alcohol and cigarette addictions in an individual in need of such treatment, comprising:

administering to the individual a therapeutically effective amount of clonidine.

2. The method of claim 1 wherein said administering is for initially between 45 and 60 days.

3. The method of claim 1 wherein said administering is transdermally.

4. The method of claim 1 wherein said administering is orally.

5. The method of claim 1 wherein said administering is via a liposomal delivery system.

6. The method of claim 5 wherein the liposomal delivery system is a nasal spray.

7. The method of claim 5 wherein the liposomal delivery system is a salve.

8. The method of claim 5 wherein the dose of clonidine delivered by the liposomal delivery system is .1 mg and at a rate of three doses per day and for twenty days.

9. The method of claim 1 wherein said administering includes using a .1 mg clonidine patch for two days and if

no adverse effects result, subsequently using a .2 mg clonidine patch.

10. The method of claim 9 wherein said administering includes after said using the .2 mg patch, using a .3 mg patch if a psychosis symptom persists and is severe.

11. The method of claim 9 wherein said administering includes after using the .2 mg patch, using a .4 mg patch if a psychosis symptom persists and is severe.

12. The method of claim 11 wherein said administering includes taking the .4 mg patch off every six to seven days.

13. The method of claim 1 further comprising conducting psychotherapy on the individual in conjunction with said administering.

14. The method of claim 13 wherein the psychotherapy involves systematic reliving of early childhood traumas (Primal Therapy).

15. The method of claim 1 wherein said administering includes applying at least one patch which includes clonidine to the individual.

16. The method of claim 1 wherein the affliction is a sleep disorder.

17. The method of claim 16 wherein said administering is via a liposomal delivery system.

18. The method of claim 16 wherein said administering includes .1 clonidine pill before bedtime for at least thirty days.

19. The method of claim 1 wherein the affliction is epilepsy.

20. The method of claim 19 wherein said administering is via a liposomal delivery system.

21. The method of claim 19 further comprising administering dilantin to the individual.

22. The method of claim 19 wherein said administering includes using a .2 clonidine patch.

23. The method of claim 19 further comprising administering reliving therapy to the individual.

24. The method of claim 1 wherein the affliction is an addiction.

25. The method of claim 24 wherein said administering is via a liposomal delivery system.

26. The method of claim 24 wherein the addiction is tobacco addiction.

27. The method of claim 26 wherein said administering uses .1 clonidine pills twice a day for approximately two weeks and then three times a day for approximately eight weeks.

28. The method of claim 24 wherein the addiction is alcohol addiction.

29. The method of claim 28 wherein said administering is via clonidine pills.

30. The method of claim 28 wherein said administering is via clonidine patches.

31. The method of claim 24 wherein said addiction is a drug addiction.

32. The method of claim 31 further comprising administering vicodin to the individual.

33. The method of claim 24 wherein said administering is via a patch of .2-.4 mg of clonidine.

34. The method of claim 33 wherein the patch is applied for 60 to 90 days.

35. The method of claim 33 wherein the patch is applied for six days.

36. The method of claim 24 further comprising in conjunction with said clonidine administering, conducting Primal Therapy to the individual.

37. A method of treating epilepsy in an individual in need of such treatment, comprising:

administering to the individual a therapeutically effective amount of clonidine.

38. The method of claim 37 wherein the epilepsy includes psychogenic type of epilepsy.

39. The method of claim 37 wherein said administering uses a patch of .2 to .4 mg of clonidine.

40. The method of claim 37 further comprising administering phenytoin sodium (dilantin) to the individual.

41. The method of claim 37 wherein said phenytoin sodium administering includes administering a pill of 100 mg of phenytoin sodium three times a day, as a cell stabilizer.

42. The method of claim 41 wherein said pill administering is for between 90 and 160 days.

43. The method of claim 37 wherein said clonidine administering includes using a patch of .2 to .4 mg clonidine.

44. The method of claim 37 wherein said administering is via a liposomal delivery system.

45. The method of claim 44 wherein the liposomal delivery system is a nasal spray.

46. The method of claim 45 wherein the nasal spray is a dosage of .2 mg clonidine, three times a day for thirty days.

47. The method of claim 44 wherein the liposomal delivery system is a salve.

48. The method of claim 47 wherein the salve is a dosage of .2 mg clonidine three times a day for thirty days.

49. The method of claim 37 wherein said administering is via a liposomal delivery system when the individual senses a seizure coming on.

50. A method of treating a compulsive eating disorder in an individual in need of such treatment, comprising:

administering to the individual a therapeutically effective amount of clonidine.

51. The method of claim 50 wherein said administering is via a pill, patch or liposomal delivery system.

52. The method of claim 50 wherein said administering is via a .2 clonidine patch for at least approximately thirty days.

53. The method of claim 50 wherein said administering is via a liposomal delivery system.

54. The method of claim 50 further comprising conducting Primal Therapy on the individual in conjunction with said administering.

55. A method of treating migraines in an individual in need of such treatment, comprising:

administering to the individual a therapeutically effective amount of clonidine.

56. The method of claim 55 wherein said administering is via a liposomal delivery system.

57. The method of claim 56 wherein the clonidine is delivered by the liposomal delivery system at a dosage of .1 mg, three times a day for approximately twenty days.

58. The method of claim 55 wherein said administering is via a nasal spray when the individual senses a migraine coming on.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06656

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 A61K9/70 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HORACEK H J: "Extended-release clonidine for sleep disorders [letter;comment]." JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY, (1994 OCT) 33 (8) 1210. JOURNAL CODE: HG5. ISSN: 0890-8567., XP002091831 United States	1,2,13, 16,18
Y	see the whole document ---	1-18
X	RUBINSTEIN S ET AL: "Clonidine for stimulant-related sleep problems [letter]." JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY, (1994 FEB) 33 (2) 281-2. JOURNAL CODE: HG5. ISSN: 0890-8567., XP002091832 United States	1,2,13, 16,18
Y	see the whole document ---	1-18

-/--

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 1999	19.04.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06656

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BABHAIR S A ET AL: "Comparison of intravenous and nasal bioavailability of clonidine in rodents." RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, (1990 FEB) 67 (2) 241-8. JOURNAL CODE: R62. ISSN: 0034-5164., XP002091833 United States see abstract ---	6
Y	CHOI Y W ET AL: "Characterization of distribution behavior of 2-imidazolines into multilamellar liposomes." JOURNAL OF PHARMACEUTICAL SCIENCES, (1991 AUG) 80 (8) 757-60. JOURNAL CODE: J07. ISSN: 0022-3549., XP000218505 United States see abstract -----	5-8

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/ 06656

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 15 (partly), 16 - 18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15 (partly), 16-18

   Use of clonidine in for the treatment of sleep disorders

2. Claims: 1-15 (partly), 19-23, 37-49

   Use of clonidine in for the treatment of epilepsy

3. Claims: 1-15 (partly), 24-36

   Use of clonidine in for the treatment of drug addiction, alcohol addiction and tobacco addiction

4. Claims: 50-54

   Use of clonidine in for the treatment of compulsive eating disorder

5. Claims: 55-57

   Use of clonidine in for the treatment of migraine